PREDICTING TIME TO DEATH AFTER WITHDRAWAL OF LIFE-SUSTAINING THERAPY IN POTENTIAL ORGAN DONORS: A SECONDARY ANALYSIS OF A MULTICENTER PROSPECTIVE OBSERVATIONAL STUDY

Department of Epidemiology, Biostatistics and Occupational Health

McGill University

Montreal, Québec, Canada

September 2018

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Master of Science.

Contents

ABSTRACT v

RÉSUMÉ vii

ACKNOWLEDGEMENTS ix

LIST OF ABBREVIATIONS xi

LIST OF TABLES AND FIGURES xii

List of tables xii

List of figures xiii

CHAPTER 1: INTRODUCTION 1

1.1. The shortage 1

1.2. The solution: donation after cardio-circulatory death 1

1.3. Barriers 2

1.4. Prediction models 3

1.5. Current study 3

CHAPTER 2: BACKGROUND AND LITERATURE REVIEW 4

2.1. History of organ donation 4

2.2. Important concepts 7

2.2.a. End-stage organ disease and organ transplantation 7

2.2.b. Deceased donation 8

2.3. Burden of organ failure 9

2.4. Barriers to donation after cardio-circulatory determination of death 10

2.4.a. Ethical concerns 11

2.4.b. Uncertainty of time to death 12

2.5. Available tools for prediction of time to death 14
2.6. Statistical analysis used in prediction of time to death studies 25
2.7. Statistical analysis used in current study 26
2.7.a. Multivariable Logistic regression 26
2.7.b. Random Forest Classification 27
2.8. Prediction modelling studies comparing multiple analysis approaches 32
CHAPTER 3: OBJECTIVES 32
CHAPTER4: OVERVIEW OF METHODS 33
4.1. Data Source: the DePPaRT study 33
4.2. Inclusion and exclusion criteria 35
4.3. Data collection-potential predictors 36
4.4. Outcome Variable 38
4.5. Statistical Analysis 38
4.5.a. Overview 38
4.5.b. Selection of potential predictors for developing models 40
4.5.c. Model development 48
4.5.c.i. The *classical* prediction model 48
4.5.c.ii. The new *classical* model 51
4.5.c.iii. The *ensemble* prediction model 51
4.5.c.iv. The new *ensemble* prediction model 53
4.5.c.v. The *univariable* model 53
CHAPTER 5. RESULTS 54
5.1. The data-set 54

5.1.a. Description of the study sample 54
5.1.b. Completeness of data 55
5.2. Developing prediction models 58
5.2.a. Model 1: The *classical* model 58
5.2.b. Model 2: The *ensemble* model 62
5.2.c. Model 3: the *univariable* model 64
5.3.a. Model 4: The new *classical* model 66
5.3.b. Model 5: The new *ensemble* model 69
5.4. Comparison of the model performances 70
5.4.a. The *classical* model vs the *ensemble* model 70
5.3.b. The *classical* vs the *ensemble* vs the *univariable* models 71
5.3.c. Comparing all five models 72
5.5. Post-hoc analysis 73
CHAPTER 6: DISCUSSION 74
6.1. Summary 74
6.2. Comparison with other studies 82
6.2.a. Predictors 82
6.2.b. Model performance 84
6.2.c. Inclusion of physician's prediction 85
6.3. Strengths and weaknesses 86
6.4. Future studies 90
CHAPTER 7: CONCLUSION 92
BIBLIOGRAPHY 94

APPENDICES 100

Supplementary Documents 122

A2. a: DePPaRT Protocol (APPENDIX 2a)

A2. b: DePPaRT Case report form (APPENDIX 2b)

ABSTRACT

BACKGROUND: Donation after cardio-circulatory death (DCD) is a vital program to address the current deficit of transplantable organs. Uncertainty about the time to death when withdrawing life support therapy is a major barrier to DCD. The primary objective of this study is to develop a new model to predict death within 120 minutes of withdrawal of life sustaining therapy (WLST).

METHODS: Prospective multicentre observational data from adult, DCD-eligible donors were analysed to develop prediction models using *a priori* selected potential predictors and two statistical approaches: *classical* multivariable logistic regression and *ensemble* random forest classification. Models were internally validated in bootstrapped samples. Model performances and physician's prediction of outcome were compared for accuracy, discrimination and calibration. Models were re-analysed with the inclusion of physician's prediction as an additional potential predictor and post-hoc univariable analysis of the included predictors were conducted.

RESULTS: Out of the included 307 eligible adult DCD donors, 57.7% died within 120 minutes of WLST. Based on the optimism adjusted area under the curve values, the *classical* models appeared to perform better than the *ensemble* models. The clinician's predictions appeared to be superior to both *a priori* models. The re-assessed *classical* model with physician's prediction and the *a priori* potential predictors, appeared to outperform all other models.

CONCLUSION: Developing efficient models including commonly assessed objective predictors is possible. Including physician's prediction improved model performances. Further exploration of the models in larger sample sizes is required.

RÉSUMÉ

CONTEXTE : Le programme de don d'organes après décès cardiocirculatoire (DDC) représente un potentiel considérable d'accroître l'offre d'organes pour pallier la pénurie pour les greffes. Il nous permettra de réduire le temps d'attente pour les greffes, de sauver des vies et d'améliorer nettement la qualité de vie d'un grand nombre de Canadiens, notamment ceux vivant avec une maladie d'organes en phase terminale. L'incertitude liée au délai écoulé entre le retrait des thérapies de maintien des fonctions vitales (TMFV) et le décès est un obstacle majeur à l'adoption du DCD. L'objectif principal de cette étude est de développer un nouveau modèle permettant de prédire le délai de décès dans les 120 minutes suivant le retrait des TMFV.

MÉTHODES : Il s'agit d'une étude analysant des données provenant d'une étude observationnelle prospective, multi-centres et multinationale, réalisée en milieu de soins intensifs auprès de donneurs DDC gravement malades, chez qui la décision du retrait des TMFV avait été prise. Les prédicteurs potentiels ont été identifiés *a priori* au début du développement des modèles et puis des deux techniques statistiques d'analyse suivantes ont été utilisées : une approche *classique*, basée sur la méthode de régression logistique et une approche *ensemble* utilisant la méthode des forêts aléatoires. Ces modèles *a priori* développés ont été évalués et comparés en fonction de la précision, de la discrimination et de la calibration, et d'une validation interne réalisée à l'aide d'échantillons bootstrappés. Ils ont également été évalués en rapport aux prévisions des médecins. Les modèles ont été ensuite modifiés en incluant les prévisions des médecins comme prédicteur potentiel supplémentaire. Ces nouveaux modèles et des modèles *a*

priori développées ont été réexaminés. Finalement, une analyse univariée post-hoc des prédicteurs potentiels a été faite.

RÉSULTATS : Parmi les 307 donneurs de DCD adultes éligibles inclus, 57,7% sont décédés dans les 120 minutes suivant le retrait des TMFV. Sur la base de la discrimination estimée par l'aire sous la courbe ROC (AUC) avec un ajustement pour l'optimisme, le modèle *classique* s'est révélé plus performant que le modèle d'*ensemble* parmi les deux modèles *a priori* développés. Les prévisions des médecins semblaient supérieures à celles des deux modèles. Lorsque les résultats ont par la suite été comparés aux deux nouveaux modèles développés incluant les prévisions du médecin, le nouveau modèle *classique* semblait être supérieur à tous les autres modèles.

CONCLUSION : Dans l'état actuel de notre analyse des modèles de prédiction développés dans cette étude, la conception de modèles efficaces comprenant des prédicteurs objectifs couramment évalués est possible. L'inclusion du prédicteur de la prévision des médecins améliore les performances des modèles développés. Une exploration plus approfondie des modèles développés ici dans des échantillons de plus grande taille serait nécessaire.

ACKNOWLEDGEMENTS

I take this opportunity to express my deep gratitude to my supervisors, Dr. Andrea Benedetti and Dr. Jason Shahin, for their guidance, constructive recommendations, and enthusiastic encouragement over the course of this study.

I would like to thank my professors whose lectures during my master's training shaped my foundation in Epidemiology, namely, Dr. Alexandra M. Schmidt, Dr. Bethany Foster, Dr. Elham Rahme, Dr. Gilles Paradis, Dr. James Brophy, Dr. Maida Sewitch, Dr. Olga Basso, Dr. Paramita Saha Chaudhuri, Dr. Scott Weichenthal, and Dr. Seungmi Yang.

I gratefully acknowledge the funding received towards my master's training from the Fonds de recherche du Québec – Santé (FRQS). I am grateful to Dr. Kevin Schwartzman for his guidance that was pivotal to my successful effort.

I would like to thank Dr. Theresa Gyorkos for her invaluable advice that prepared me and helped in keeping my progress on schedule.

I express my gratitude to Dr. Sam Shemie, and Dr. Sonny Dhanani for this learning opportunity. I am grateful to the entire DePPaRT study team who made this study possible. I specially thank Amanda van Beinum, Laura Hornby, Melanie Hogue and Dr. Nathan Scales for their help in enabling me to familiarize with the study and the dataset.

I take this opportunity to thank my cohort and seniors, for their support in helping me develop my skills with R- software from the scratch, especially Elizabeth Kunke, Gabrielle Simoneau, Luc Villandré, Marichelle Leclair, Mohammed Rashid, and Yi Lian. I would like to express my sincere gratitude to my friends and colleagues, especially Ayan Kar, Deyvid Alvarez Evaristo, Dr. Marina Amaral De Avila Machado, and Mohammad Sazzad Hasan, for

participating in discussions to help me think through various challenges that I faced during data cleaning. I would like to recognise the guidance from Brice Lionel Batomen Kuimi and Luc Villandré that helped me improve my ability to encapsulate this study effectively in the French language.

I express my deepest gratitude to my Department for their support, in the face of unforeseen challenges. I specially thank André Yves Gagnon, student affairs administrator, and Katherine Hayden, student affairs coordinator, for their compassionate guidance through these challenges that created a stress-free environment and helped me focus on the completion of this study.

Finally, I take this opportunity to express my unfathomable gratitude to my parents for their prayers and sacrifices, all my teachers for their patience and encouragement, and my well wishers for believing in me.

LIST OF ABBREVIATIONS

APACHE II	Acute physiology and chronic health evaluation II
AUC	Area under the curve
BMI	Body mass index
BP	Blood pressure
CART	Classification and regression trees
CT	Computed tomography
DCD	Donation after cardio-circulatory death
DCD	Chinese Donation after Circulatory Death (Nomogram)
DCD-N	Donation after cardiac death-neurological
FiO2	Fraction of inspired oxygen
GCS	Glasgow coma scale
IABP	Intra-Aortic Balloon Pump
ICU	Intensive care unit
ITU	Intensive treatment unit
OOB	Out of bag
PaO2	Partial pressure of oxygen
ROC	Receiver operating characteristic curve
SaO2	Oxygen saturation
UNOS	United network for organ sharing
UWDCD-ET	University of Wisconsin donation after cardiac death evaluation tool
WLST	Withdrawal of life-sustaining therapy

LIST OF TABLES AND FIGURES

List of tables

TABLE 1: Scoring method proposed in the DCD-N model 19

TABLE 2: Probabilities of death within 60 min according to the combinations of predictive variables in the DCD-N model 20

TABLE 3: Proposed scoring method for the predictive model developed by Brieva et.al. 22

TABLE 4: Risk factors and predictors associated with time to death ($p<0.05$) 42

Table 5: Characteristic of study population 56

TABLE 6: The *classical* multivariable logistic regression model with *a priori* selected potential predictors 59

TABLE 7: Evaluation of the *classical* model 60

TABLE 8: Performance indices from bootstrap validation of the *classical* model 60

TABLE 9: Evaluation of the *univariable* model 65

TABLE 10: Performance indices from bootstrap validation of the *univariable* model 65

TABLE 11: The new *classical* model 67

TABLE 12: Evaluation of the new *classical* model performance 68

TABLE 13: Performance indices of the new c*lassical* model 69

TABLE 14: Comparison of model performance: the *classical* model vs the *ensemble* model 71

TABLE 15: Comparison of model performance: the *classical* model vs the *ensemble* model vs the *univariable* model 72

TABLE 16: Comparison of all five prediction models developed 73

APPENDIX TABLE 1: Post-hoc univariable logistic regression and description of the potential predictors by outcome 110

List of figures

FIGURE 1: Classification tree not using ICU specialist prediction (Brieva et. al., 2014) 22

FIGURE 2: Classification tree using ICU specialist prediction (Brieva et. al., 2014) 23

FIGURE 3: DCD-C Prediction tool 25

FIGURE 4: Scoring method proposed in the DCD-C model 25

FIGURE 5: Diagrammatic representation of random forest classification 31

FIGURE 6: Schematic overview of the population included in the study 55

FIGURE 7: Importance of predictors from the *ensemble* model 64

FIGURE 8: Important predictors from the new *ensemble* model 70

APPENDIX FIGURE 1:The United Network for Organ Sharing (UNOS) Criteria 102

APPENDIX FIGURE 2: The University of Wisconsin DCD Evaluation Tool (UWDCD-ET). 103

APPENDIX FIGURE 3: Correlation matrix (Pearson) 107

APPENDIX FIGURE 4: Correlation matrix (Spearman) 108

APPENDIX FIGURE 5: Receiver operating characteristic curve of the *classical* model with *a priori* potential predictors 109

APPENDIX FIGURE 6: Plot of error rate vs number of trees for tuning the *ensemble* model with *a priori* selected predictors 112

APPENDIX FIGURE 7: Plot of error rate vs *mtry* at optimum number of trees selected for tuning of the *ensemble* model with *a priori* selected predictors 113

APPENDIX FIGURE 8: Receiver operating characteristic curve (ROC) and area under the curve (AUC) for *ensemble* random forest classification model with *a priori* predictors (Training-set) 114

APPENDIX FIGURE 9: Receiver operating characteristic curve (ROC) and area under the curve (AUC) for *ensemble* random forest classification model with *a priori* predictors (Test-set)..... 115

APPENDIX FIGURE 10: Receiver operating characteristic curve (ROC) and area under the curve (AUC) for *univariable* model with physician's prediction as predictor 116

APPENDIX FIGURE 11: Receiver operating characteristic curve (ROC) and area under the curve (AUC) for the new *classical* model with *a priori* selected and physician's prediction as potential predictors..... 117

APPENDIX FIGURE 12: Error plot vs number of trees for tuning new *ensemble* model 118

APPENDIX FIGURE 13: Plot error rate vs *mtry* for tuning the new *ensemble* model..... 119

APPENDIX FIGURE 14:Figure 12: Receiver operating characteristic curve (ROC) and area under the curve (AUC) for new *ensemble* random forest classification model *with a priori* predictors and new predictor of physician's prediction (Training-set) 120

APPENDIX FIGURE 15: Receiver operating characteristic curve (ROC) and area under the curve (AUC) for new *ensemble* random forest classification model with *a priori* predictors and new predictor of physician's prediction (Test-set) 121

CHAPTER 1: INTRODUCTION

1.1. The shortage

Over the past two decades, the growing shortage of transplantable organs globally has been a rising concern leading to the World Health Organization calling for nations to promote organ donation (The Madrid resolution on organ donation and transplantation: national responsibility in meeting the needs of patients, guided by the WHO principles, 2011). Currently, over 4,500 Canadians are awaiting an organ transplantation. Not all patients in need of an organ make it to the waiting list. In Canada, the shortage persists at 2.5 times the available organs for transplants (Terner, 2016). For a patient awaiting an organ transplant, this translates to a 30–40% probability of not receiving an organ over their lifetime (Munshi L, 2015). In 2016, for every Canadian who received an organ, there was another on the waitlist in need of one. This figure does not account for those who died in waiting or were removed from the list as their condition deteriorated while waiting and as a result, or those who were no longer considered eligible for transplantation (Canadian Institute of Health Information. e-Statistics Report on Transplant, Waiting List and Donor Statistics, 2014, 2016). Reflection of this disparity is visible in Quebec as well. As of December 31st, 2017, Transplant Quebec reported 786 recipients on the waiting list. While documented deaths from lack of transplantation was reported among 54 expectant recipients, these numbers do not capture all patients who were removed from the waiting list as they were no longer considered eligible (Statistiques officielles 2017, 2018).

1.2. The solution: donation after cardio-circulatory death

Technological advances in organ preservation has buoyed the practice of donation after cardio-circulatory death (DCD). Organ donation with DCD is applicable in patients who have

suffered a terminal non-recoverable injury but are not brain dead. In these patients, organ donation follows declaration of death assessed by the cessation of cardio-circulatory activity. In critically ill patients, where a decision has been made towards the withdrawal of life sustaining therapy (WLST) by their surrogate decision makers and their health care team members, life sustaining therapy is stopped while continuing comfort measures. In patients who have expressed their consent to donate their organ(s) and when patient's surrogate decision makers have confirmed such a consent, the transplant team is informed. A dedicated team then coordinates patient evaluation for organ donation and enables a prompt organ procurement upon death of the patient. The transplant team is in a state of readiness to conduct organ retrieval in the shortest interval, minimizing organ damage from cessation of circulation to the organ following death of the donor. DCD allows organ donation from patients who would otherwise be refused since they do not meet organ donation criteria of brain-death.

In 2006, following global adoption of DCD to increase organ transplantation, Canada embraced DCD after much deliberations. Nevertheless, Canada continues to lag globally in organ donation rates. In the 2016 System Progress Report Update, Canada recognises the crucial role of DCD in enabling Canadian donors to fulfill their wish and help those on the transplant wait lists

1.3. Barriers

Time to death following WLST is critical to successful organ donation in DCD. Periods of time to death post WLST greater than two hours causes organ damage rendering them unsuitable for transplantation (Shemie SD, 2006). The unpredictability of the time to death is one of the main barriers to broader acceptance of DCD. This is evident from reports that

approximately 20-30 % of consented donors do not die within outlined time limits for DCD. This results in unmet family expectations and consumption of hospital resources (Munshi L, 2015). An accurate prediction tool to assess time to death after WLST is required to identify potential DCD donors, inform family on the likelihood of successful donation, inform end-of-life care decision making, minimize emotional distress for families and for healthcare providers, and optimize hospital resource.

1.4. Prediction models

There have been few attempts to address the need for such a prediction tool. Inadequate sample size, lack of external validity or issues of generalizability to all eligible DCD donors have impeded the widespread adoption of the few existing prediction tools (Munshi L, 2015). In most of the available tools, specific observations obtained after removing patients from ventilatory support for a duration of ten minutes are requirement for assessment. This has been a major concern in application of the two most commonly quoted tools. Two other proposed tools are applicable in neuro-critical patients specifically. A suitable model to predict time to death within 120 minutes of WLST would not only ameliorate current DCD donation practises, it would also lead to the development of standardised practices and would enable comparison of studies to inform future DCD organ donation practices.

1.5. Current study

This is the first Canadian study to propose the development and validation of a novel prediction model to predict time to death within 120 minutes after WLST in critically ill adults. This study would analyse data from a prospective multicenter observational study among potential DCD donors undergoing WLST. This study builds on existing understanding in the

field of organ donation, contributes in the quest for a generalised prediction model for successful DCD donations to positively impact the lives of Canadians and millions globally.

CHAPTER 2: BACKGROUND AND LITERATURE REVIEW

2.1. History of organ donation

Modern medicine records the first transplant in 1869 when a Swiss surgeon performed a successful skin transplant. The First attempt at solid organ transplant is reported in 1906 where a kidney transplant using a porcine source was unsuccessful. The first attempt at human kidney transplant was undertaken in 1936. The initial attempts at liver, lung and heart transplantations date back to the 1960s, while the first pancreas transplant was in 1978, followed by the first intestine transplant in 1987. Success in bone marrow transplant between siblings had been already achieved in the 1950s using total body irradiation for immunosuppression. This approach was used in kidney transplants without much success. The first successful kidney transplant was carried out between identical twins to address the issue of immunosuppression in 1954. The discovery of immunosuppressant effects of ciclosporin marked the beginning of the modern immunosuppressive era from the mid-1970s onwards. This contributed to the first successful liver transplant roughly two decades after the first attempt.

Despite marked improvement in surgical techniques, immunosuppression and organ storage, the success of organ transplantation was, and continues to be, largely dependent on the viability and health of the organ. This was historically demonstrated by the pioneers of organ transplantation over the course of many unsuccessful attempts. The initial organs were harvested from donors who had died with cessation of cardiac activity and who had their organs

subsequently harvested. It became apparent that the main determinant of organ viability was the degree of ischemia (lack of blood flow) that was incurred during the harvesting process. When the donors heart stops beating and blood flow to the organ has ceased, ischemia and organ damage ensues. The time from death to organ procurement needs to be as short as possible so that the organ can be preserved. The initial attempts at organ harvesting occurred many hours after the death of the donor, allowing for ischemia to set in and damage the organ. Organ ischemia was a major barrier in the 1960's that prevented the widespread use of organ transplantation. With this realization, there was a new focus on the definition of death and specifically brain death.

Until the late 1950s-early 1960s, ascertaining if a person was dead was mostly done by examining the heart and lungs for irreversible cessation of life-sustaining activities. In the late 1950s with the advent of critical care units and cardio-pulmonary life support, it became possible to sustain circulation and cardiac activity in an individual who suffered a severe brain injury (for example from a stroke or cerebral hemorrhage). Whereas previously these patients would die, they were now being maintained on a mechanical ventilator with good cardiac function all the while with a severely injured brain. Removal from cardio-pulmonary support would result in cardio-pulmonary collapse and subsequent death. Among these patients there were some who had sustained very severe brain injury or whose conditions had deteriorated leaving them with seemingly no brain activity. At what stage could these patients be considered to be already in the process of dying or dead, was a difficult question to answer. Clear guidelines were needed to bring transparency to the practice in modern critical care. Finally, in 1968, the Ad-Hoc Committee of the Harvard Medical School examined the issue and reported on the criteria for

ascertaining irreversible coma, thus defining brain death (A definition of irreversible coma. Report of the Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death, 1968). It was established that despite ongoing cardiac activity, patients who had severe enough brain damage as diagnosed through a neurological exam or vascular imaging study could be officially considered dead. Following this new definition of death, non-heart-beating donation, which was the only source of grafts from deceased donors, came to be replaced by donors who met brain death criteria. The main reason why organ donation from patients who had a neurological determination of death came to be the dominant source of organs is that despite being dead, the donors had preserved cardiac and respiratory function and were therefore able to maintain perfusion of their organs. The problem of organ ischemia that plagued transplants with grafts from deceased donors had now become a non-issue.

It was clear by the 1980s that organ transplantation was a viable option for people with irreversible organ failure. The new problem that developed was that due to the success of transplant programs with newer surgical techniques and better immunosuppression and donors who were brain dead and not prone to organ ischemia, the need for organs outstripped the supply. To support the increasing shortage some patients, risked travelling internationally to receive an organ. Transplantation tourism was increasingly found to be supported through illegal and unethical practises of organ-trading leading to the declaration of Istanbul on Organ Trafficking and Transplant Tourism, 2008 (Participants in the International Summit on Transplant Tourism and Organ Trafficking, 2008) . This summit was convened after a direction issued by the World Health Assembly in 2004 “to take measures to protect the poorest and vulnerable groups from transplant tourism and the sale of tissues and organs, including attention

to the wider problem of international trafficking in human tissues and organs" (Eighth plenary meeting-Committee A, 2004). The need to develop of an organ donation programme based on DCD to legally and ethically expand the donor pool led Canada to re-examine DCD. Countries like United States, United Kingdom, Spain, Netherland, Switzerland and Japan were among countries to already have established protocols for DCD and had experienced significant increase in their organ transplantations.

With a growing understanding of how to limit the organ ischemia, DCD has re-emerged as a viable option for organ donation. Aside from increasing the donor pool, DCD has enabled non-brain-dead willing donors to fulfil their wish to donate their organs and bring life-saving remedies to the rising number of people with organ failure. This has also empowered grieving families to carry out their loved one's last wishes and in turn bring them some comfort during their bereavement period.

2.2. Important concepts

2.2.a. End-stage organ disease and organ transplantation

End stage organ failure is characterized by an organ that has permanently lost its ability to perform its homeostatic functions causing the individual to either die or be dependent on temporary external support measures for day-to-day survival.

Transplantation is the process where healthy organs and tissues are retrieved from a donor and implanted in a suitable recipient in order to replace a missing or irreversibly damaged organ. A donor can donate several tissues: musculoskeletal grafts that include bones and tendons, cornea, skin, heart valves, nerves, veins, and blood stem cells which include bone marrow,

peripheral blood and umbilical cord blood. Donatable organs include heart, kidneys, liver, lungs, pancreas and intestine. Depending on the type, organs can be donated during the life time of a healthy donor, also known as living donation or upon death of donor, also known as deceased donation. Organ transplantation is the only treatment for end-stage diseases of the liver, heart and lung, and the best therapy in the case of end-stage renal disease. A single deceased donor can potentially save up to 8 lives and can help up to 75 individuals through solid organ (lungs, heart, liver, kidneys, pancreas and bowel) and tissue (eye tissue, heart valves, bone, tendons, veins and ligaments) donation. Depending upon the circumstances of death, deceased donation could be classified as donation after neurological determination of death (NDD), also known as post-brain-death donation, or donation after cardio-circulatory determination of death (DCD), also known as non-heart-beating donation.

2.2.b. Deceased donation

The primary rule for organ donation states that organs can only be procured from donors who are dead; this is otherwise known as the dead donor rule. Following this, deceased donation can follow either after confirmation of brain death or cardiac death. Donation after neurological determination of death (NDD) occurs when patients who have suffered severe brain damage but still have preserved cardiac and hemodynamic activity are eligible to donate organs such as heart, lungs, liver, kidneys, pancreas or small intestine after their physician has determined that all brain activity has ceased. It is differentiated from donation after DCD and there may not be conclusive evidence of cessation of all brain activities. The usual scenario of a DCD donation involves a critically ill patient who has suffered a devastating disease but is not brain dead. After

all measures have been exhausted and it is felt that the patient's disease process is not survivable with an adequate quality of life, the patient's loved ones, in-keeping with patient's wishes and in-discussion with treating team, may decide for WLST. Upon withdrawal of the life sustaining therapy and the demise of the patient, the transplant team has to procure and preserve the organ(s) for donation in the shortest possible interval to minimize organ ischemia.

Ever since Canada adopted DCD, it has continued to contribute significantly to the increase in Canadian transplantation rates and constituted 23% of the total number of deceased donations in 2016.

2.3. Burden of organ failure

Terminal organ failure is associated with poor outcome, significant adverse effects and considerable cost to the healthcare system (Vasiliadis HM, 2005) (Gagnon YM, 2004) (Taylor MC, 2002). A growing elderly population, rise in chronic diseases like diabetes, hypertension and metabolic syndrome, chronic Hepatitis-C virus infection, and cancer are among the main reasons behind the growing number of patients with terminal organ failure. Recognized as the ultimate form of curative therapy for irreversible organ failure, it has become imperative for the main stakeholders in the Canadian health care system to pay close attention to the rate of organ failures amongst the Canadian population and donor organ availability (Dossetor JB, 1999).

In Canada, roughly five deaths per week occur that would be avoided if these individuals were transplanted with a viable organ in time. Replacing the failing organ with a healthy organ becomes the only reliable solution in such individuals for an opportunity to return to normal daily living. Globally, in 2015, a 5.8% increase in solid organ transplantations was registered

from the previous year. Although this amounted to roughly 126,670 solid organ transplants, this number is estimated to reflect only about 10% of the global need. (Transplantation, 2017).

While the majority (76%) of Canadians awaiting organ-transplants needed a kidney transplant, there is also an increasing need for liver (10%), lungs (6%) and heart (4%) transplants.

In addition to good clinical outcomes, studies among renal transplantation patients observed significant health care cost savings, increased availability of resources previously utilized by the transplanted patients and increased productivity and contribution to the economy by the transplanted patients (The Economics of Kidney Failure, p. 2012).

Deceased donation is the unequivocal leading avenue of organ transplantation globally (Organ donation and transplantation in Canada- System progress report 2016 update, 2017). In Canada, deceased donation provides for about 77% of all transplants (Organ donation and transplantation in Canada-System progress report 2006-2015, 2016).

2.4. Barriers to donation after cardio-circulatory determination of death

Canadian Council for Donation and Transplantation (CCDT) developed the medical, ethical and legal framework for DCD through the collaboration of the Canadian Association of Transplantation, the Canadian Society of Transplantation, and the Canadian Critical Care Society (Shemie SD, 2006). The first DCD organ transplant was carried out in 2006. The recent increase in Canada's national donation rate is contributed by increasing numbers of DCD donors. Provinces with established DCD programs are expanding their programs to further increase

donation rates. These include Ontario, Quebec, British Columbia, northern Alberta (Edmonton) and Nova Scotia. While Saskatchewan documented its first DCD transplantation in 2015, Manitoba is geared for its first DCD transplantation and southern Alberta(Calgary) is preparing to start its DCD program (Organ donation and transplantation in Canada-System progress report 2006-2015, 2016). Despite the available framework for DCD it has not been fully adopted across the country for the following reasons:

2.4.a. Ethical concerns

One of the hotly debated points around the practice of DCD is how much time is needed to elapse post circulatory arrest before the declaration of death can be made and the organs procured. Currently, after withdrawal of life support therapy has happened and the patient has died, as evidenced by the cessation of a blood pressure reading, there is a 5 minute "no touch" period. The no touch period is in effect so that clinicians can monitor the patient for any recurrence of life. If none are seen, then procurement of organs can ensue. The basic premise and rule of organ donation is that no organs can be taken from a patient who is alive; this is otherwise known as "the dead donor rule". All organ donation programmes stem from this one ethical principal. The "no touch period" is in place to make sure that the DCD donor is in fact dead prior to organ procurement. The ethical debate revolves around the duration of the no-touch period to rule out an event of autoresuscitation. Critics of DCD suggest in favour of longer wait times before initiation of organ procurement after arrest of circulation. In fact, different hospital around Canada and the world have different policies for wait times ranging from 2 minutes to 10 minutes. These wait times are not purely academic as longer wait times mean more organ ischemia and potentially poorer patient outcomes. On the flip side shorter wait times may mean

violating the dead donor rule. Existing evidence in literature is inconclusive, thus raising the need to study the process of dying post WLST in greater details to establish transparent rules in determination of death. the Canadian Critical Care Trials Group supported the "Determination of Death Practices in Intensive Care Research Program" (DePPICt) Program as the first observational study to prospectively collect waveform data for 30 minutes after the declaration of death (Dhanani S. et.al., 2014). This pilot study conducted among 41 subjects observed that persistence of cardiac electrical activity with the documented absence of circulation may not be relevant to declaration of death and recommended further evaluation.

Under the current global shortage situation facing nations, programs will seek initiatives to provide viable remedy. The aspects of social acceptability of medically and ethically responsible methods of donor eligibility assessment is a continuing debate. As technology evolves, it will enable better understanding and help to strengthen standardized transplantation procedure protocols and transparent communication grounded in medically, ethical and socially acceptable principles.

2.4.b. Uncertainty of time to death

Time to death is the period following WLST and until declaration of death. According to current DCD guidelines a declaration of death is made upon confirmation of cessation of cardio-circulatory function. A successful organ donation concludes with retrieval of organ(s) that is in good health and which upon transplantation into a recipient would resume functioning. The period up to the infusion of cold organ preservation fluid is referred to as warm ischemic time. In all instances, with the initiation of WLST in a consenting donor, a dedicated organ transplant

team is on stand-by to proceed with organ procurement immediately upon ascertainment of occurrence of death in donor. In cases of marked perfusion deterioration from prolonged withdrawal phase warm ischemia, even if organs are promptly perfused with cold preservation solution upon death, the organs could be already severely damaged, thus, making any transplantation effort unavailing. As a result, studies focus on time to death, to assess donation eligibility.

Determination of death following cardio-pulmonary arrest can take place either in the situation of a patient under intensive care and upon WLST, or where a patient cannot be revived through cardio-pulmonary resuscitation either on the way to the Emergency or in a hospital. These patients may not be brain death and so the brain death criteria cannot be used to determine death to make organ donation ethically acceptable. In these patients DCD makes organ donation possible by upholding dead donor rule. To be considered for retrieval, kidneys need to have a minimum functional ischemic time of 120 minutes, as compared to 60 minutes for lungs and 30 minutes for liver and pancreas. As a result, upon WLST, organ retrieval teams are required to call-off the procedure only after the duration of warm ischemia time rules out the possibility of viable organs from donor. In UK 40% (Manara et.al 2012 BMJ DCD paper) of organ retrieval efforts from DCD donors are aborted, on average, concurrent to time to death observations (Munshi L, 2015). While a center in UK assessed that increasing wait time to 4 hours, could potentially add 30% to the count of retrieved kidneys while upholding acceptable standards of transplantation outcomes (Reid A.W.N., 2011), such a blanket waiting-time rule could potentially come at a cost of inefficient use of finite healthcare resources. Definitions, assessment and confirmatory criteria for death in DCD have been found to differ between

countries (Rogers W.A., 2011). Interestingly, they have even been found to vary within a country, whether within health set-ups locally (Rhee J.Y., 2011) or those by localities (Fugate J.E., 2011). In the absence of a validated tool to assess time to death after WLST, it is difficult to build consensus practice which adopt standardized optimum pathways. Such a prediction tool would enable robust eligibility assessment towards stream-lined processes while also allowing for continuous evaluation, re-assessment and evolution of global standard practice of DCD with respect to evolving technology and comorbidities.

2.5. Available tools for prediction of time to death

As, discussed above, the inability to predict time to death prior to WLST is a key barrier to broader DCD use in Canada and worldwide. There have been several studies describing the risk factors associated with time to death following WLST with even fewer studies that have developed risk prediction tools. By and large these tools make use of patient clinical and physiological characteristics at the time of WLST to predict time to death.

In North America, there are two prediction tools that are referred to for DCD practice, namely, the University of Wisconsin Donation after Cardiac Death Evaluation Tool (UWDCD-ET) and the United Network for Organ Sharing (UNOS) scoring systems (APPENDIX 1a, 1b). These tools had never been externally validated and were developed using small sample sizes. The UWDCD-ET is geared for the non-brain dead critically ill patients with severe irreversible neurological injury whose family and care team have come to the decision to WLST (Lewis. J et.al., 2003). Scores are calculated based on observations obtained upon disconnecting the patient from ventilatory support for 10 minutes (otherwise known as an apnea trial) and are then used to

predict time to death within 60 and 120 minutes and assess suitability for DCD. While the tool is simple for clinical use, the requirement of disconnecting a patient from the ventilator for 10 minutes makes it unsuitable to assess patients who do not have severe neurologic defects or hemodynamically unstable patients and those who are heavily dependent on ventilator support. The UNOS and UWDCD-ET do not include neurological assessment data. The variables that are used to calculate the score and derive probabilities of death within 60 minutes following WLST include age, spontaneous respiratory rate, tidal volume, negative inspiratory force and oxygen saturation (after 10 minutes off ventilator), vasopressor/inotrope use and endotracheal tube or tracheostomy tube intubation status.

The UNOS scoring systems consensus committee developed the UNOS criteria based on expert opinion to assess DCD eligibility with respect to predicting death within 60 minutes after WLST. The UNOS criteria consist of a number of factors which include: respiratory rate; use of cardiac assist device (left ventricular assist device/ right ventricular assist device/ arterio-venous extracorporeal membrane oxygen/ veno-venous extracorporeal membrane oxygen), pacemaker unassisted heart rate, peak end expiratory pressure (PEEP) and oxygen saturation (SaO2), fraction of inspired oxygen (FiO2), vasopressor/inotrope use, cardiac index and use of intra-aortic balloon pump (IABP).

Studies attempting to validate these tools in their study population found them to be not readily applicable. Coleman et. al. found the modified UWDCD-ET to be poor predictor of time to death post WLST though a modified UNOS predicting tool showed significant association (Coleman, Brieva, & Crowfoot, 2008) in their study sample of 81 patients. In the study by DeVita et. al., where they validate the UNOS criteria in their study sample, they also propose the

development of alternate criteria for easy application and to improve prediction of death within 60 minutes of WLST (DeVita M.A, 2008). They analyzed a sample of 505 patients who underwent WLST, where only 95 patients were qualified as 'desirable donor candidates'. Death within 60 minutes of WLST, occurred in 45% of both their total WLST population and the 'desirable donor' sub-group. The new rule proposed by DeVita et. al., was derived by using parametrical estimates of the probability of death within 60 min using both regression tree (CART) analysis and stepwise forward regression. Their prediction model requires the Glasgow Coma Scale (GCS), a combination of SaO2/FiO2 ratio and peak inspiratory pressure derived from the ventilator, to predict if donor is likely to die within 60 minutes of WLST. Requirement of vasopressors and spontaneous respiratory rate off-mechanical-ventilation were added to the rule to increase its sensitivity and specificity. Their model demonstrated very high sensitivity and negative predictive value in the smaller 'desirable donor' subgroup, while specificity and positive predictive values were modest in comparison. Despite acceptable performance of their new rule, the authors were not able to overcome the hurdle of input from an apnea test as is needed in the cases of the UWDCD-ET or the UNOS tool.

The apnea test off ventilation is not a widely accepted practice in ICUs internationally, causing concerns over the application of prediction tools of UNOS and UWDCD-ET (Brieva J. et.al, 2014). This indicates the likelihood of reliance on intensivist's expert opinion for prediction of death within 60 minutes being applied in most cases. In view of concerns over apnea test requisition for available tools, several studies have been conducted to identify potential predictors and there have been several attempts at developing new tools that will find greater clinical applicability.

In 2009, Suntharalingam et. al. conducted a multicenter study in UK renal transplant centers to identify predictors of death within 60 minutes of WLST (Suntharalingam C., 2009). Withdrawal of life support therapy comprised of simultaneous cessation of respiratory support (ventilator or extubation) along with inotropes. The study included 191 potential donors about to undergo WLST, irrespective of transplantation outcome. Only about 7.9% of the potential donors had undergone apnea test (required for application of UNOS and UWDCD-ET) and out of the 99 potential organ donors who donated their organs, death within 60 minutes of WLST was observed in only 15.2%. Using Kaplan–Meier plots and log-rank statistics, the authors observed that neurological injury, pre-WLST mode of ventilation, age, inotrope use, FiO2 and pH at WLST were found to influence time to death in this group of potential donors. Younger age, higher FiO2 and mode of ventilation were the strongest influencers of time to death.

Studies in end-of- life-care have also assessed risk factors that influence time to death after withdrawal of life-sustaining support in critically ill patients seeking comfort care in the face of imminent death. Cooke et.al. found nonwhite race (hazard ratio [HR] 1.17; 95% confidence interval [CI]: 1.01-1.35), number of organ failures (per organ HR 1.11; 95% CI: 1.04-1.19), vasopressors (HR 1.67; 95% CI: 1.49-1.88), IV fluids (HR 1.16; 95% CI: 1.01-1.32), and surgical vs medical service (HR 1.29; 95% CI: 1.06-1.56) to be predictors of a shorter time to death in their study population (Cooke, Hotchkin, & Engelberg, 2010). The female sex and older age groups emerged as predictors of longer time to death. The study included patients who died in the hospital ICUs or 30 hours post-ICU discharge. Though 93.2% of the patients died within 24 hours, time to death extended up to 6.9 days in the study population that included multiple centers in the US. In a single center study in the US by Huynh et.al., fraction of inspired

oxygen (FIO2) >70% (HR 1.92; 95% CI: 1.24–2.99) and requirement for vasopressors (HR 2.06; 95% CI: 1.38–3.09) were found to be associated with shorter time to death and being on the neurology/neurosurgical service at the time of ventilator withdrawal was associated with a longer time to death (HR 0.60; 95% CI: 0.39–0.92). (Huynh, M. Walling, Le, & Kleerup, 2013). Patients withdrawn from the ventilator, as a part of palliative care, were less likely to be on the surgery service and more likely to be on the neurology/neurosurgical service in their study cohort. Roughly half of the study patients died while continuing to be on mechanical ventilation, and in roughly half the population, palliative withdrawal of mechanical ventilation was administered.

Yee et. al. retrospectively studied severely injured neurological patients admitted to the neurology ICU who would be eligible for DCD donation (Yee A.H. et. al., 2010). In order to avoid potentially risking acute irreversible organ damage from a temporary cessation of ventilation necessary for apnea test, the authors used a combination of variables without doing an apnea test to predict time to death. Yee et. al. identified 4 clinical variables, corneal reflex, cough reflex, motor response and that of oxygenation index, to be independently associated with death within 60 minutes post WLST. Abnormal findings corresponding to these variables would signal potentially severe irreversible brainstem dysfunction regardless of etiology. Multiple risk factors relating to the patients cardiac, neurologic and respiratory state showed independent association on univariable analysis, but only the 4 potential predictors emerged to be statistically significant upon multivariable analysis. The proposed assessment calculates increasing probability of earlier death upon WLST subject to presence of number and combination of the 4 factors. The authors suggest inclusion of these variables in future prediction models. Rabinstein et. al. (Rabinstein

A.A. et.al., 2012) , conducted a multicenter prospective cohort observational study among 178 patients wherein 46% died within 60 minutes of WLST. The authors developed a practical score, DCD-N (TABLE 1), for assessment of potential candidates for DCD in patients with non-survivable brain injury based on the variables proposed in the study by Yee et. al. According to their tool, patients with a score of 3 or higher (TABLE 2) were predicted to die within 60 minutes of WLST with a sensitivity of 72%, specificity of 78%, PPV of 74% and NPV 77%.

TABLE 1: Scoring method proposed in the DCD-N model

Component	Points
Absent corneal reflex	1
Absent or extensor motor response to pain	1
Oxygenation index of more than 3·0	1
Absent cough reflex	2

In the Netherlands, Wind et.al. studied 211 potential donors, wherein 161 patients died with 60 minutes of WLST (Wind J. et.al, 2012). They used multivariable binary logistic regression analysis and found that only controlled mechanical ventilation remained as a significant risk factor to predict death within 60 mins. Time to death post WLST ranged from 1 minute to 3.8 days, while 76% of the patients died within the first hour after WLST. Clinicians predicted death within 60 minutes in the study sample with a sensitivity of 73% and specificity of 56% (receiver operating characteristic curve- area under the curve [ROC-AUC] of 0.646; 95% CI: 0.556 - 0.737), while for death within 120 minutes with respective sensitivity and specificity of 89% and 25% (AUC of 0.571; 95% CI: 0.456 - 0.686). Their model performed better at predicting death within 60 minutes and 120 minutes of WLST compared to prediction from

intensivists. The model predicted death within 60 minutes with a sensitivity of 70% and specificity of 74% (AUC of 0.738; 95% CI: 0.656 - 0.819), and for death within 120 minutes with respective sensitive and specificity 84% and 53% (AUC of 0.775; 95% CI: 0.693- 0.857). The authors concluded that in their assessment, donor eligibility could not be determined with acceptable certainty, either dependent on intensivist's prediction or that from models examined, and they proposed initiation of donation process in every potential donor.

TABLE 2: Probabilities of death within 60 min according to the combinations of predictive variables in the DCD-N model

Absent Corneal reflex	Absent Cough reflex	Extensor or absent motor response	Oxygenation index >3·0	Score	Probability
No	No	No	No	0	0.08
No	No	No	Yes	1	0.16
Yes	No	No	No	1	0.18
No	No	Yes	No	1	0.20
No	Yes	No	No	2	0.26
Yes	No	No	Yes	2	0.34
No	No	Yes	Yes	2	0.37
Yes	No	Yes	No	2	0.40
No	Yes	No	Yes	3	0.45
Yes	Yes	No	No	3	0.48
No	Yes	Yes	No	3	0.51
Yes	No	Yes	Yes	4	0.61
No	Yes	Yes	Yes	4	0.71
Yes	Yes	Yes	No	4	0.74
Yes	Yes	Yes	Yes	5	0.87

Formula used in the DCD-N model:
Logit = –2·49 + (0·90 × absent corneal reflex) + (1·65 × absent cough reflex) + (0·98 × extensor or absent motor response) + (0·12 × oxygenation index)

Brieva et. al. developed a new classification rule to predict death within 60 minutes of WLST in a DCD eligible Australian donor population. In their first study (Brieva J. et.al., 2013),

using multivariable regression analysis and statistically significant variables from univariable analysis, they developed two multivariable explanatory models to predict death within 60 minutes of WLST. The two models differed on the inclusion of a variable for specialist's prediction. One included it, while the other did not (TABLE 3) Variables included in the multivariable analysis have been summarized the TABLE 3 included: acute physiology and chronic health evaluation (APACHE) score, GSC, ICU days, days on mechanical ventilation, systolic and diastolic blood pressure (BP), mean arterial pressure, arterial oxygen saturation, number of patient triggered breaths on pressure support ventilation, PEEP, liver function test (LFT), chest radiograph, oliguria, creatinine, sedation use, analgesia use, and vasopressor/ inotrope use. Both the final models included the following six variables: number of patient triggered breaths on pressure support ventilation, GCS, PEEP, systolic BP, pH, no analgesia. In a follow-up study, using a development sample of 159 DCD eligible donor population, Brieva et. al. derived two prediction models usin0g only three predictive ‘‘rules’’ with CART analysis. One of their classification rules included intensivist's individual expert prediction of death with 60 minutes of WLST (FIGURE 1, 2). The efficiency, sensitivity and positive predictive value of this model was found to be comparable to using ICU specialist prediction alone (a single classification rule) (Brieva J. et.al, 2014). Their other model that did not include clinician prediction as a predictor, demonstrated sensitivity of 82%, specificity of 59% and PPV 68 % (AUC of 0.78) for the model developed with logistic regression and sensitivity of 71% and PPV of 77% for the one using CART. Model performance for the models developed with the inclusion of clinician prediction as a predictor demonstrated slightly better sensitivity of 84%,

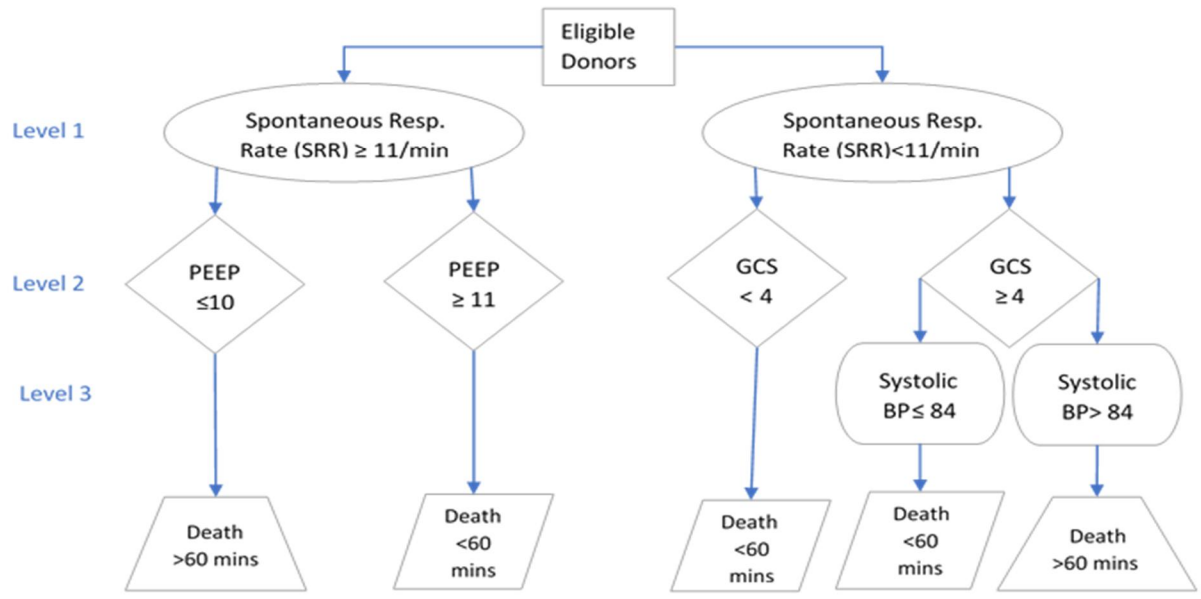
specificity of 72% and PPV of 77% (AUC of 0.84) for the logistic regression model and sensitivity of 82% and PPV of 80% for the CART model.

TABLE 3: Proposed scoring method for the predictive model developed by Brieva et.al.

Component number	Component	Score			
1	Spontaneous respiratory rate	0	≥ 11	+1	≤ 10
2	Glasgow Coma Scale	0	≥ 4	+1	3
3	Positive end-expiratory pressure	0	≤ 10	+2	≥ 11
4	Systolic blood pressure	0	≥ 105	+1	85-104
				+2	≤ 84
5	pH	0	≥ 7.33	+1	7.25–7.32
				+2	7.15–7.24
				+3	≤ 7.14
6	Analgesia	0	Yes	+1	No
7	ICU specialist predicts death ≤ 60 minutes	0	>60 minutes	+2	≤60 minutes

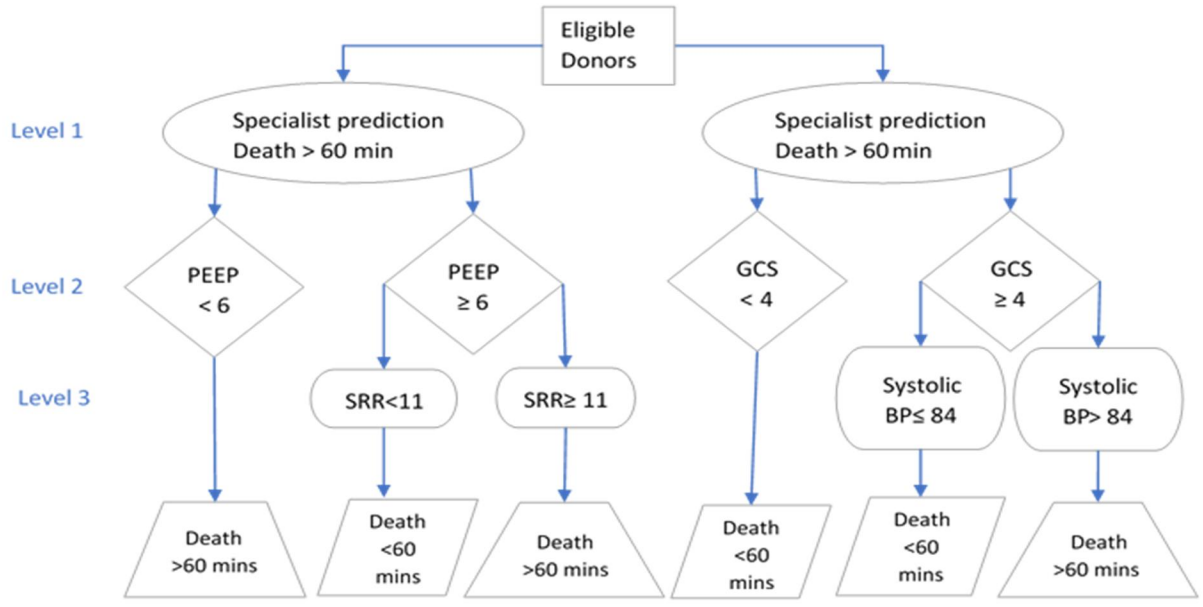
*Prediction model *index 1 scored by summing weights for each component (1–7) and* Prediction model *index 2 by summing (1–6).*

FIGURE 1: Classification tree not using ICU specialist prediction (Brieva et. al., 2014)



BP = blood pressure
GCS score = Glasgow coma scale
PEEP = peak end-expiratiry pressure
SRR = Spontaneous respiratory rate

FIGURE 2: Classification tree using ICU specialist prediction (Brieva et. al., 2014)



BP = blood pressure
GCS score = Glasgow coma scale
PEEP = peak end-expiratiry pressure
SRR = Spontaneous respiratory rate

While most studies were aimed at developing prediction tool for death within 60 minutes of WLST in controlled DCD donors in the ICU, where apnea test may or may not be advised, there were studies that aimed at predicting outcome of health of retrieved organ from such donors. Davila et. al. proposed a model to predict cardiac arrest post WLST among potential donors and for graft usability in the Netherlands in the context of liver transplantation (Davila D. et.al, 2012). In their study population, they observed that 73% of accepted donors experienced cardiac arrest post WLST. Post WLST cardiac arrest was observed in the younger donors on inotrope support and were those with higher levels of serum sodium and creatinine and associated with mostly absent of cough/ gag reflex. Davila et. al. found that variables of donor age, BMI, length of ITU stay, warm ischemia time and alanine transaminotransferase levels are predictive of graft usability, using conditional multivariable binary forward logistic regression.

More recently, He et. al. developed a model in the Chinese population, referred to as DCD-C Nomogram (FIGURE 3, 4), incorporating 10 routinely available variables into a nomogram as an alternative model for predicting the time to death after WLST in neurocritical patients (He X. et. al., 2015). Predictor variables were selected based on evidence from literature and expert opinion from clinical practice of the authors in the context of neurocritical patients. Variables selected from univariate and subsequent multivariate analyses were used to develop a nomogram, which is a simple graphical representation of a statistical predictive model that creates a numerical probability of a clinical event. Variables included in the nomogram were: hospitalization days, pupil size, pupil reflex, corneal reflex, cough reflex, motor response to pain, cisterna ambiens (a sheet-like curved layer of subarachnoid space extending from the cisterna quadrigeminalis and partially encircling the midbrain on each side, connecting with the cisterna interpeduncularis), swirl sign (non-contrast CT appearance of low attenuation or radiolucency inside intracranial hyperattenuated hematomas), brain herniation, and intraventricular hemorrhage. The DCD-C Nomogram reported consistent high c-index (AUC) in training, external validation and prospective validation cohorts. Xu et.al. report DCD-C Nomogram's superior c-index (AUC) in comparison to DCD-N, UNOS and UWDCD-ET assessment tools. In China, brain death is not an accepted concept and in contrast DCD is widely accepted by the people leading to majority of deceased donation being DCD donations. Also, according to the practice, confirmatory tests of brain death like electroencephalograph, somatosensory evoked potentials and transcranial Doppler are not strictly adhered to due to unavailability across community health centers there. Routinely, brain death is assessed clinically in patients suffering irreversible coma of known origin with absent spontaneous ventilation and brain stem reflexes.

FIGURE 3: DCD-C Prediction tool

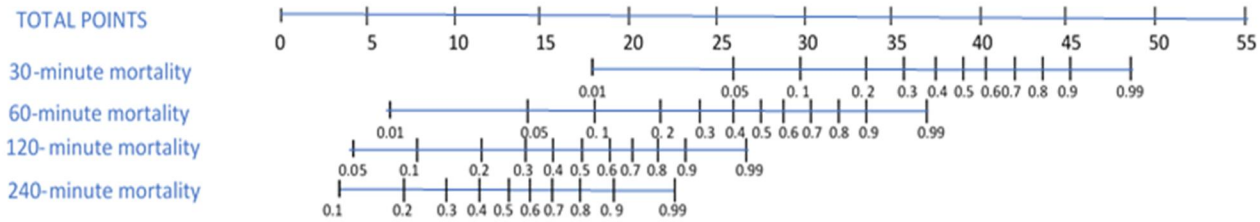
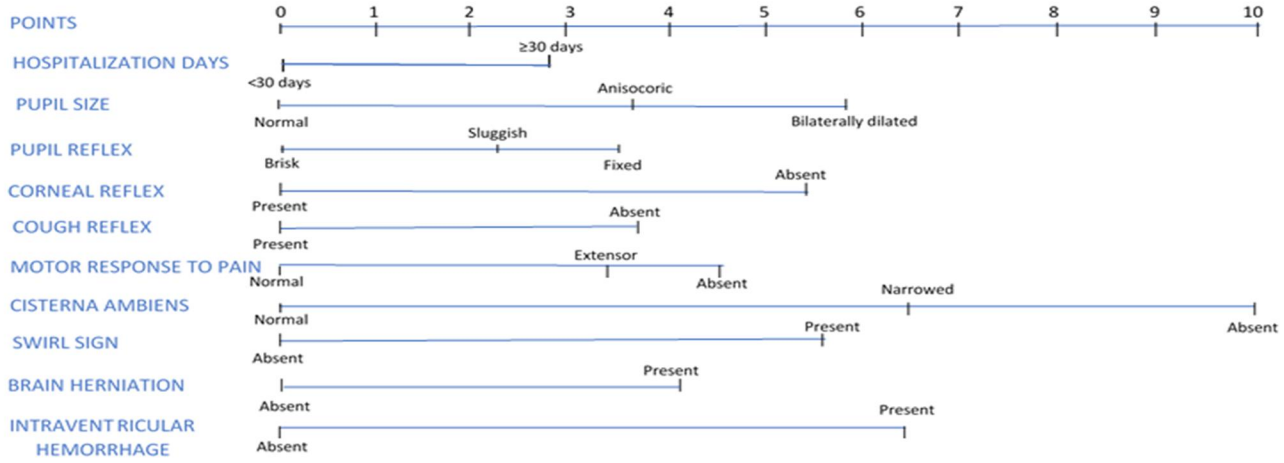


FIGURE 4: Scoring method proposed in the DCD-C model



2.6. Statistical analysis used in prediction of time to death studies

In the studies described above, multiple statistical approaches were adopted. The initial UNOS tool was developed based on expert opinion. The two-stage process of multivariable

logistic regression modelling where significant variables are obtained from a univariable analysis of potential predictors has been employed in multiple studies (Wind J. et.al, 2012) (Brieva J. et.al, 2014) (Yee A.H. et. al., 2010). Other methods included Cox regression and CART analysis (Brieva J. et.al, 2014). In the DCD-C study, Kaplan–Meier survival curves were generated and compared using the log-rank test and statistically significant variables were further analyzed through a Cox regression model. A nomogram was then formulated from this multivariable analysis to enable clinical use (Rabinstein A.A. et.al., 2012) (He X. et. al., 2015).

2.7. Statistical analysis used in current study

2.7.a. Multivariable Logistic regression

Logistic regression, developed by statistician David Cox in 1958, (Cox, 1958) is a special scenario of generalized linear model where the dependent variable (outcome) is a binary categorical variable, indicating success or failure of outcome (or, presence or absence of event) in the study sample under analysis. In cases where the possible outcomes may be more than two, a multinomial logistic regression is applied. In cases where the dependent variable is categorical in an ordered fashion, ordinal logistic regression is applied.

Logistic regression is a logit model, used to explain the relationship between the binary dependent variable and one (univariable) or more (multivariable) continuous or categorical independent variables. The model estimates the log of odds of the probability of event occurring

$$Log_e\left[\frac{P(Y=1|X_1,\ldots,X_p)}{1-P(Y=1|X_1,\ldots,X_p)}\right]=Log_e\left[\frac{\pi}{1-\pi}\right]=$$

$$=\alpha+\beta_1X_1+\ldots+\beta_pX_p=\alpha+\sum_{j=1}^{p}\beta_jX_j$$

as a linear combination of independent variable. In other words, in logistic regression, the dependent variable is a probability of the occurrence of the event of interest. So, in a logistic regression, the degree of certainty is a function of how much information we have, which are captured by the variables added to the model.

The independent variables included in the model could be chosen based on evidence or expert opinion or based on statistical significance demonstrated upon univariable analysis. Even though independent variables might be statistically significant in univariable analysis, they may or may not be statistically significant when included with other variables. While including more and more information (in the form of variables) in a model, always allows a model to capture the relationship closely, thus improving the its ability to predict the results closely, but after a certain number of variables (parsimonious), there is no significant improvement observed in model performance with any additional variable. There are various methods to arrive at this parsimonious model, either by starting with the full model that includes all the variables and moving in a backward step-wise manner, continuously removing the variable that is least contributory. Model building can also be approached by starting from the null model, that contains only the intercept with a variable being added in a forward step-wise manner. Model building can also be approached by using a combination of forward and backward methods.

2.7.b. Random Forest Classification

Random forest classification is comparatively a newer addition to analytical tools in bioinformatics and is being increasingly applied in the field of medicine. Leo Breiman and his colleagues developed a new statistical procedure, Classification and Regression Trees (CART)

(Breiman L. et. al., 1984). Based on the data, CART creates a decision tree in an attempt to identify a strategy that would help it arrive at the outcome of interest (positive event or an outcome category). The algorithm of decision making in CART is like a flow chart and at each node the data is split based on the response of a test, producing two branches, each of which represent a test outcome leading to the next node or test in a cascading series of possible outcomes of deciding factors leading to leaf nodes that represents a class label (decision taken after computing all attributes) (FIGURE 2). Random Forests were later introduced by Leo Breiman as an extension of his idea of 'bagging' (Breiman L., 2001) in an attempt to make more accurate (more informed) predictions than would be possible through the experience of any individual learning experience (a model). Bagging is an approach of machine learning, where the idea is to draw upon the predictions from multiple learning algorithms to learn by combining all these learning experiences (also recognized as 'ensemble learning'). A sampling technique called 'bootstrapping' is used for these multiple learning experiences. In bootstrapping, multiple samples are created by randomly selecting each sample of the same size as the study sample but selected with replacement from the total known observations of the study sample data. These phantom samples from bootstrapping vary from the original study sample data, given that in each iteration of drawing such samples with replacement some data points would be duplicated, while some others would be dropped over the large number of repetitions. Thus, bootstrapping is a generic statistical technique to approximate the sampling distribution for a particular statistic, using resampling with replacement, while bagging is a method of aggregated learning using bootstrapping (also called "bootstrap aggregating").

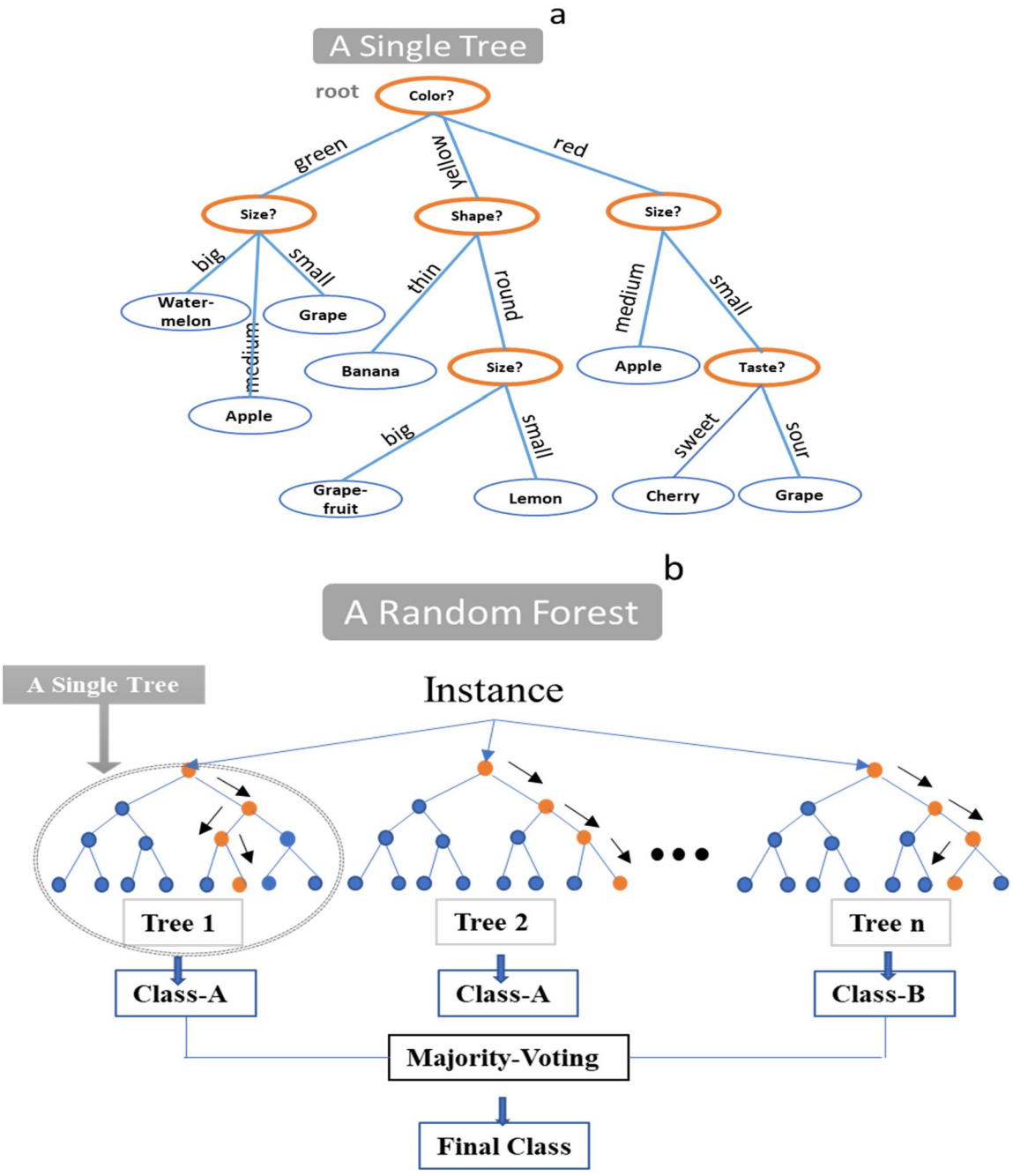
Leo Breiman combined both new and existing ideas to describes this method of statistical analysis by applying 'ensemble' learning method for classification (also regression), which would construct multiple decision trees and output the modal class (mean in the case of regression) of individual trees. This method is known to correct overfitting to their training set, which was a not so desirable finding with decision trees. Using bootstrap samples, a decision tree is grown to its greatest depth minimizing the loss function (FIGURE 5). At each node, best split of decision tree is chosen from random sample of input variables instead of all variables. The study data is split into training and testing subsets. Repeated random sub-sampling of the training data are used, which will on average contain 63.2% of the study data while the rest are replicates. For each tree, using the leftover (36.8%) data, *out-of-bag* (OOB) error rate or the misclassification rate is calculated. Aggregate error from all trees is used to determine overall *out-of-bag* error rate for the classification.

The idea of splitting each node using a random subset of available decision from the data was introduced by Amit and Geman (Amit Y., 1997). They introduced the idea of searching over a random subset of the available decisions when splitting a node in the context of growing a single tree. The idea of the decision at each node being selected by a randomized procedure, against a deterministic optimization was influenced by the work of Dietterich (Dietterich T., 2000) who introduced randomized node optimization. The unique aspect of random forest was most influenced by the work of Ho and his colleagues (Ho T.K., 1998). Ho proposed the idea of growing a forest of trees wherein variation among the trees is introduced using randomly chosen subspace of the training data before fitting each tree or each node, also called random subspace selection. Computationally, Random Forests naturally handle both regression and (multiclass)

classification and can be used directly for high-dimensional problems. They depend only on one or two tuning parameters, easily be implemented in parallel and are relatively fast to train and to predict. They have a built-in estimate of generalization error as *out-of-bag* error and are also statistically appealing by providing additional measures such as variable importance, differential class weighting, missing value imputation, outlier detection, visualization, and can be applied to unsupervised learning.

In summary, when the random forest classification algorithm is applied to data, it first subsets the data by selecting square root of the number of columns. It also takes a bootstrap sample of the rows of data and the algorithm will create as many subsets as is the number of trees specified. Then, it creates a decision tree using each subset of data and computes a prediction. A final prediction is computed based on the results of these individual predictions. It continues building a forest of uncorrelated trees using a CART like procedure, in conjunction with randomized node optimization and bagging (bootstrap aggregating).

FIGURE 5: Diagrammatic representation of random forest classification



a (Bijoy V.T., 2013)*; b.* (Koehrsen, 2017)

2.8. Prediction modelling studies comparing multiple analysis approaches

Prediction tools have come to play an important role in modern medicine facilitating early detection and intervention opportunity towards better patient outcomes. This helps healthcare efficiency, transparent communication and decision making by incorporating evidence-based knowledge from clinical practice and being able to apply to a specific patient scenario. Recent studies in prediction modelling have compared results from applying more than one tool to arrive at the best model for a given dataset. Random Forest classification has been observed to outperform multivariable binary logistic regression analysis in multiple studies (Chen R., 2015) (Peng S.Y., 2010) (Prosperi M.C., 2014). No previous studies of predicting time to death post WLST in DCD donors have used Random Forest classification. Brieva et.al. and DeVita et. al. used the CART analysis while multivariable binary logistic regression analysis has the been most often used method. In this thesis, both multivariable binary logistic regression and random forest classification have been applied to the dataset from a prospective multicenter observational study on withdrawal of life-sustaining therapy in critically ill patients.

CHAPTER 3: OBJECTIVES

The primary objective of this study is to develop a prediction model for predicting time to death within120 minutes from WLST among critically ill DCD eligible patients undergoing WLST using commonly assessed objective measures. The developed prediction model aims at generalizability and simplicity to enable clinical application in DCD eligible critically ill patients across institutions and countries with ease and accuracy.

CHAPTER4: OVERVIEW OF METHODS

4.1. Data Source: the DePPaRT study

This study analyses data from the ongoing "Death Prediction and Physiology after Removal of Therapy- DePPaRT" study (APPENDIX 2a). The DePPaRT study, a multi-centre, prospective, observational, longitudinal cohort study, is aimed to primarily study the natural history of cessation of physiological function, after the withdrawal of life sustaining therapy (WLST), in adult and pediatric patients to inform the criteria to ascertain permanent cessation of neurologic and cardiac function after cardiac arrest following WLST. The DePPaRT study includes critically ill patients >1 month of age and in whom imminent death was anticipated following a decision to withdraw life-sustaining support made by patient's family and treating team. Patients in whom declaration of death would be assessed through brain-death criteria or who had a functioning pacemaker or in whom informed consent was not available, were excluded. Informed consent was obtained in accordance with the International Council for Harmonisation guidelines and institutional research ethical boards guidelines.

Among those meeting inclusion criteria, a purposive sampling strategy was used to recruit patients. Purposive sampling is a method of deliberately choosing patients, with aim to reach a targeted sample quickly and in a manner that is reflective of the range of cases relevant to the event of study-interest. Purposive sampling requires the knowledge of the characteristics of the underlying population and the study objective. In the DePPaRT study, employing this kind of sample design was intended to provide as much insight as possible into the event or cardiac arrest and eventually death following WLST in critically ill patients. Some of these patients are required to be eligible and successful DCD donors, while others would need to represent those

eligible while not successful and the remaining would be those who would not qualify for DCD. This type of sampling technique is also referred to as judgmental, selective, or subjective sampling wherein sampling for proportionality is not the main concern. The DepPaRT study was targeting a sample that would include a minimum of 10% and maximum of 40% patients who would represent "DCD non-eligible" patients. "DCD eligible" patients could represent a minimum of 10% to a maximum of 80% of enrolled patients and "DCD patients" would represent a minimum of 10% and maximum of 40% of the study population. "DCD non-eligible" patients were those who satisfied study inclusion criteria but not those for DCD donation. "DCD eligible" patients were those that satisfied both study inclusion and DCD donation criteria irrespective of materialization of an organ donation. Conditions required for the materialization of an organ donation in a consenting eligible patient would be inclusive of: the availability of DCD donation facility at the center, declaration of death by DCD guidelines within specific time limits conducive for organ retrieval practice at the center.

Based on review of literature, 60% of the enrolled patient population was expected to comprise DCD eligible patients, notwithstanding whether these patients proceeded with the procedure of DCD donation. Patient demographic information was gathered from observations documented during a period commencing one hour prior to WLST, until declaration of death and 30 minutes after declaration of death. Information of administered treatment during this period along with events during WLST were gathered in great details. Events relevant to the current analysis that were collected during WLST included the following: initiation of withdrawal, the first support withdrawn and sequence of withdrawal of support, manner of withdrawal as reflected through an abrupt end to support or a sequence of tapering doses of support drug or

equipment adjustments. All patient data was captured through case report forms (APPENDIX 2b) with de-identification of patient information and assignment of a study ID. Patient data were then uploaded to a database in a secure website, http://www.deppart.org.

The DePPaRT study was primarily developed by Dr. Sonny Dhanani (primary investigator) and Dr. Sam Shemie. Dr. Jason Shahin is the lead investigator for a DePPaRT sub study exploring prediction of time to death following WLST and contributed to the conceptualization and study design. The DePPaRT study also benefitted from advisors which included Dr. Andrew Seely (information technology), Jane Chamber-Evans (ethics), Dr. Teneille Gofton (neurology), and Dr. Tim Ramsay (statistical analysis/study methodology). The methodology and analysis for the current thesis has been developed and executed by the author (Dr. Shamistha Biswas) under the guidance of thesis supervisors Dr. Andrea Benedetti and Dr. Jason Shahin.

4.2. Inclusion and exclusion criteria

For the current study, all enrolled adult patients who were 18 years and older and who met DCD eligibility by standard and/ or extended criteria were included in the analysis. To be eligible by standard criteria would require a consenting DCD donor to not be positive for any of the following: >79 years of age; active or remote melanoma; active malignancy; metastatic malignancy or high-grade brain tumour; serious unresolved sepsis or systemic infection; intravenous drug abuse; human T-cell leukemia-lymphoma virus; systemic viral infection (measles, rabies, etc.); prion related disease; and herpetic meningoencephalitis.

4.3. Data collection-potential predictors

Data was collected at multiple time points of the patients stay in the ICU which included baseline demographic and characteristics at ICU admission as well as physiological and clinical parameters at one hour prior to WLST. Potential predictors were then chosen from these collected data. The collected data included the following: age, sex, admission diagnosis, comorbidities, BMI, severity of illness, vasopressor and analgesia dosing at one hour prior to WLST, manner of WLST, CT head findings, ventilatory mode, respiratory rate, physician's prediction. Admission diagnosis was categorized as: traumatic brain injury (all poly trauma cases were included here), non-traumatic brain injury neurologic conditions, medical and other non-traumatic surgical diagnosis. Comorbidities were categorized as: respiratory, cardiac, neurologic, and others. BMI was categorised as ≥ 30 or < 30. Patient status data collected at ICU admission was used to calculate APACHE II score according to guidelines (Knaus W.A., 1985). Baseline (at one-hour prior to WLST) opioid analgesic doses were converted to morphine equivalent dose expressed as mg/kg/hr. These included doses in patients who were either already on such medications as a drip, notwithstanding if stopped at baseline or continued beyond, or received as a bolus dose at baseline. The British Columbia guidelines were followed for conversion factors was used to calculate the dose (Guidelines and Protocols Advisory Committee, 2017). To calculate the ratio of partial pressure of oxygen (PaO_2) to fraction of inspired oxygen (FiO_2) at WLST, PaO_2 values from blood gas analysis from only arterial blood were included.

Data were reviewed from a randomly selected sample of enrolled patients to evaluate administered interventions along the timeline of interest. It was our observation that in a large number of reviewed patients, the time stamp denoting the decided 'initiation of WLST' did not

coincide exactly with intervention modifications to reflect such initiation. While in some instances, this might have been a logistical lag between documentation and administration of intervention in an intensive care setting, in others it captures variations in administering WLST. These variations ranged from simultaneous withdrawal to staggered withdrawal. WLST was re-defined as a 40-minute window, starting from 20 minutes before the documented 'initiation of WLST' time stamp and extending to 20 minutes post the recorded 'initiation of WLST' time stamp. For more than one available FiO2 value in the newly defined WLST window, the first available value was included as the FiO2 at (at the beginning) of WLST. CT findings were grouped by subachnoid hemorrhages, hematoma (subdural or epidural) and brain hemorrhage or intracerebral hemorrhage or intraventricular contusion or hemorrhage, with or with out the presence of cerebral oedema; brain tumours and brain Infections with or without the presence of cerebral oedema; and as only cerebral oedema. Mode of ventilation at WLST was categorized to be not spontaneous for control modes with same set and actual respiratory rates. When actual respiratory rate was greater than set rate for on-support modes were categorized as spontaneous modes. Among extubated patients, where time of declaration of death was greater than 10 minutes post extubation, spontaneous respiration was assumed.

Data on prediction of time to death made by physicians was also collected. Physicians indicated their level of confidence as low, medium or high against their prediction of an event of death occurring in the windows of one, two, six and twelve hours from WLST. Predictions with a confidence of moderate or high, for event of death in one and two hours windows were included as prediction of occurrence of event of death by the physician. In the past, studies have used ICU specialist opinion on time to death as an individual predictor (Brieva J. et.al, 2014;

Brieva J. et.al., 2013) in their predictive models. In the current study, an *a priori* decision was made to evaluate physician's predictions as a separate univariable model, and in sensitivity analysis of the models developed using the two approaches which were later assessed in a dataset including the predictor along with all initial *a priori* selected potential predictors.

4.4. Outcome Variable

The primary outcome is death within 120 minutes following WLST. The primary outcome was decided *a priori* based on current clinical practice and DCD guidelines of organ procurement within a maximum of 120 minutes of warm ischemia time. Time- to-death was defined as the time between the initiation of WLST and declaration of death. Initiation of WLST was defined by the first act of extubation, cessation or weaning of vasopressors or weaning of ventilator settings. The bedside clinical team was responsible for the formal declaration of death.

All DePPaRT study subjects who were either not DCD eligible or below 18 years of age were excluded from analysis in the current study. Irrespective of assigned status upon inclusion to the DePPaRT study, all subjects in whom eligibility could not be concluded from available data were also excluded.

4.5. Statistical Analysis

4.5.a. Overview

For this study, the statistical analysis plan was drawn up *a priori* and involved using different statistical approaches to develop and validate the prediction models using *a priori* selected potential predictors. The following two approaches for model development were

employed: a) a multivariable logistic regression approach and b) a statistically driven, random forest classification approach. The first two models were developed using selected predictors from a pool of potential predictors. The *classical* multivariable logistic regression model was developed using thirteen potential predictors while the *ensemble* random forest classification model was developed using all 22 *a priori* selected potential predictors. These potential predictors were chosen *a priori* through a systematic literature review and a survey of clinician's expert opinion. No statistical selection would be employed in the modelling phase and once chosen, all *a priori* potential predictors were retained in the model.

The physician's prediction of outcome was studied as a third *univariable* model. The predictor was modelled as the only predictor for the outcome of death within 120 minutes of WLST. This was done to compare the model prediction performances to those of the physicians'. Following this third model, two more models were developed with the inclusion of physician's prediction as an additional predictor to the first two models. The new *classical* and new *ensemble* models would continue to retain their respective approaches and *a priori* selected predictors and differ from their earlier versions only in the addition of the physician's prediction to the potential predictor. These new models were then compared to the three earlier models.

After all model development had occurred a univariable analysis of the association between individual potential predictors and the outcome was undertaken. All statistical analysis was performed using R Statistical Software [version 3.5.0 (2018-04-23); R Foundation for Statistical Computing, Vienna, Austria].

4.5.b. Selection of potential predictors for developing models

Selecting potential predictors based on an initial assessment of effect size in the study sample and step-wise elimination is a common observation in developing prediction models (Walter & Tiemeier, 2009). These methods have been extensively criticized in the literature in view of overfitting, exaggerated effect size estimates and bias (Steyerberg, 2009), (Greenland, 2008). However, these techniques have been found to be used in studies on prediction of time to death post-WLST (Yee A.H. et. al., 2010), (Brieva J. et.al., 2013), (Brieva J. et.al, 2014). Selection of predictors is ideally recommended before studying the predictor–outcome relationship. Two suggested approaches of predictor selection are to use subject knowledge, and to study the distribution of predictors in the data under study. A list of 5–20 candidate predictors is considered reasonable to develop an adequate predictive model (Steyerberg, 2009). In this study, an *a priori* decision was made to use the recommended method and refrain from any predictor-outcome relationship assessment and statistical effect-size assessments prior to the completion of model development. Candidate predictors were identified based on a review of the literature on risk factors and prediction models predicting time to death post WLST in patients admitted to an ICU. Using the identified candidate predictors from the literature, a questionnaire was prepared and disseminated to Canadian and international organ donation specialists to survey expert opinion on the importance of these predictors in WLST (APPENDIX 3). Using a combination of the survey results and the literature search a final list of potential predictors was developed.

Studies that performed both univariable and multivariable analysis on potential predictors were examined (TABLE 4), with higher consideration given to predictors emerging through

multivariable analysis (Steyerberg, 2009). Age, indices of oxygen requirement and respiratory distress, hemodynamic parameters, level of consciousness, severity of illness and ICU length of stay are among predictors that have been assessed to be potential predictors in existing literature (TABLE 4). Pupillary reflex, though assessed, has not been used in many models. While other brain stem reflexes have been included in existing models, pupillary reflex was found to be a commonly measured physical exam finding in the critically ill compared to other reflexes and therefore more feasible to collect. In the study by Cooke et. al. (Cooke, Hotchkin, & Engelberg, 2010) , they recommended exploring measures of acute severity of illness as a predictor. As such, we included the APACHE II score in our data collection as it is the most widely used severity of illness score in the ICU literature. Furthermore, the study by Coleman et. al. found APACHE II score to be associated with time to death post WLST (Coleman, Brieva, & Crowfoot, 2008) . The potential predictor of presence of cardiac arrest, defined in this study as an incident necessitating resuscitation, was included as a potential predictor based on clinical intuition and discussion of the comorbidity indices in existing literature. Inclusion of height as potential predictor was based on studies exploring relationship between height and mortality arising from respiratory diseases, coronary heart disease, stroke and predisposition to cancer (He, et al., 2014). Patient's race, ethnicity, and socio-economic background, in addition to sex, could also potentially influence patient's height. In the study by Cooke et. al. (Cooke, Hotchkin, & Engelberg, 2010) race and sex were found to be independent risk factors of time to death after WLST. Information on patient's race was not available in the current study. Height, along with sex, was included among *a priori* potential predictors as a potential surrogate. All selected potential predictors were included in the questionnaire for expert opinion feedback.

TABLE 4: Risk factors and predictors associated with time to death (p<0.05)

Risk Factors/ Predictors	Risk Factor analysis		Prediction tool	
	Univariable Analysis	Multivariable Analysis	Univariable Analysis	Multivariable Analysis
Demographic and disease process variables				
Age	R2, R4	R2, R4	P3	P3, P7
Sex	R2	R2		
Race	R2	R2		
Education	R2	R2		
BMI			P3	P3, P7
Admission diagnosis	R2$^{\varphi}$, R3 $^{\varphi}$	R2 $^{\varphi}$, R3 $^{\varphi}$	P2	
Comorbidities	R2		P5*, P8	P8
Charlson/ Deyo comorbidity score	R2			
APACHE II score		R1	P1, P2	
AIDS	R3			
Hospitalization days			P4	
ICU length of stay			P1, P2	P3
Health insurance status	R2			
Respiratory variables				
Controlled spontaneous respirations (mode)	R4	R1, R4	P6, P8	P8
Spontaneous RR			P1, P2, P6	P1b, c, P2a, b, P7
Respiratory Rate (actual rate = set rate)			P5	
Positive end expiratory pressure	R3		P1, P2, P6	P1a, b, c, P2a, b
FiO2	R3, R4	R3, R3	P6	
PaO2				P6a, b
Oxygenation index			P4, P5, P6†	P5, P6†a, b
Arterial oxygen saturation			P1, P2, P6	P7
Duration of mechanical ventilation			P1, P2	
Chest radiograph			P1, P2	
PaO2/ FiO2 ratio			P5, P6	
PIP			P6	P6a, b
Minute ventilation	R3			
Negative inspiratory force				P7
Tidal volume				P7
Endo-tracheal tube			P6	P7
Hemodynamic variables				
Systolic blood pressure	R4	R1	P1, P2, P5$^{\#}$, P6	P1a, b, c, P2a, b
Pulse rate			P6	
Vasopressors	R2, R3, R4‡	R1, R2, R3	P1, P2, P6‡, P8‡	P6‡a, b, P7, P8‡

Risk Factors/ Predictors	Risk Factor analysis		Prediction tool	
	Univariable Analysis	**Multivariable Analysis**	**Univariable Analysis**	**Multivariable Analysis**
Organ failure	R2[±]	R2[±]	P6[±]	P6a[±±]
Liver function test			P1, P2	
GGT			P3	
ALT			P3	P3
Bilirubin			P3	
Coagulopathy			P5	
Urea			P1	
Creatinine			P1, P2, P3	
Pre-WLST IV fluids	R2	R2		
Dialysis	R3			
Diastolic blood pressure			P1, P6	P6a, b
Mean arterial Pressure			P1, P2	
Oliguria			P1, P2	
Neurologic variables				
Glasgow coma scale		R1	P1, P2, P6	P1a, b, c, P2a, b, P6a, b
Cough/gag reflex			P4, P5	P4, P5
Corneal reflex			P4, P5	P4, P5
Absent/ extensor motor response			P4, P5	P4, P5
Pupil size			P4	P4
Pupil reflex			P4, P5	P4
FOUR score			P5	
Brain reflexes (count of reflexes absent)			P8	
Neurologic deficit			P8	
Analgesia			P1, P2	P1a, b
Sedation			P1	
CT Scan				
Cisterna Ambiens			P4	P4
Effacement of basilar cisterns			P5	
Swirl sign			P4,	P4
Brain Herniation			P4	P4
Intraventricular hemorrhage			P4	P4
Stroke/ Hemorrhage			P5 (>2 location)	
Metabolic variables				
pH	R4		P1, P2	P1a, b, c,
ABG			P5	
Sodium			P5	
Potassium			P3	

Risk Factors/ Predictors	Risk Factor analysis		Prediction tool	
	Univariable Analysis	Multivariable Analysis	Univariable Analysis	Multivariable Analysis
Chloride			P4	
UNOS criteria				
Apnea/ Respiratory rate			P6	P6a, b
PEEP≥ 10 and SaO2≤ 92%		R1[Å]	P6	
FiO2≥ 0.5 and SaO2≤ 92%		R1[Å]	P6	
Norepinephrine/ phenylephrine ≥0.2			P6	
Dopamine≥15			P6	
IABP1:1 or (dobutamine or dopamine ≥10 and CI ≤ 2.2)			P6	
Number of UNOS criteria		R1	P6 (≥1)	
Simultaneous WLST/ within 10 min			P6	P6b
Endo-tracheal tube withdrawal				P6b
Any comfort medication (within 1hour pre-withdrawal)			P6 [µ]	P6 [µ] b
Neuromuscular blockade (within 24 hours of WLST)			P6	P6
Others				
Warm ischemia time			P3	
Cause of death	R4			
Physician opinion		R1	P1, P2	P1a, P2a

Risk facto/ predictor studies:
R1- Coleman et. al. (2008)
R12-Cooke et. al. (2010)
R3-Huynh et. al. (2013)
R4-Sundaralingam et. al. (2009)

Prediction model studies:
P1-Brieva et. al. (2013)
P2-Brieva et. al. (2014)
P3-Davila et. al. (2012)
P4- [DCD-C] He et. al. (2015)

Prediction model studies:
P5- [DCD-N] Yee et. al. (2010)
P6-Devita et. al. (2008)
P7-Lewis et. al. (2003)
P8-Wind et. al. (2012)

R1-Associated variables for death within 60 minutes after palliative WLST in critically ill patients
R1[Å] Oxygenation disruption= SaO2 < 92% with a PEEP of > 10 cmH2O or an FIO2 > 0.5.
R2-End- of-life care study in patients for terminal withdrawal of life-support.
R2φ admission diagnosis= Primary Service at time of death
R2± organ failure= Non-pulmonary organ failure
R3- Palliative withdrawal of mechanical ventilation study in imminently dying patients
R3 φ admission diagnosis= Primary Service
R4-Time to death study in potential DCD organ donors.
R4‡ vasopressors= Inotropes

P1- death within/ after 60 minutes from WLST
P1a-including ICU specialist prediction
P1b-excluding ICU specialist prediction
P1c-ICU specialist prediction
P2- death within/ after 60 minutes
P2a- including ICU specialist prediction
P2b- excluding ICU specialist prediction
P3- graft usability prediction model included here
P4- death within 60 minutes from WLST in neurocritical patients
P5- neurology ICU; death <60 minutes from WLST
*P5*comorbidities= gastro and renal disease*
P5# systolic blood pressure= hypotension

P6- death within 60 minutes of WLST
P6† Oxygen index= SaO2/ FiO2
P6‡ Vasopressor= use and dose (at withdrawal)
P6 µ any comfort medication= includes morphine, fentanyl, Propofol, lorazepam, midazolam and hydromorphone
P6 ± organ failure= includes infection, shock, and status post cardiac arrest
P6a- only patient characteristics
P6a±± organ failure= hepatic failure
P6b- (P6a & withdrawal process predictors)
P7- Wisconsin Tool criteria
P8-death with 120 minutes of WLST model included here
P8‡ Vasopressor= Norepinephrine

The potential predictors were screened for completeness of data, variation and correlation for selecting the pool of potential predictors to be used for model development. Variation in the distribution of the potential predictors was assessed using standard deviation, inter quartile range, and visual representations. Potential predictors with range of observations representative of the range observed in the study population, were preferred over tighter distributions. After excluding potential predictors with greater than 25% missing data, the remaining were ranked by weight from the literature review and the results of the survey of the clinical expert. The top 22 potential predictors were chosen to form the final pool to be used for model development. This was considered a reasonable pool based on the recommended number of about 5–20 candidate predictors for develop an adequate predictive model (Steyerberg, 2009). All these 22 predictors were used for the *ensemble* models. These consisted of the following: age, BMI, APACHE II score, admission diagnosis, comorbidities, GCS at WLST, pH, ventilation support mode, blood pressure, respiratory rate, vasopressor use, PaO2, FiO_2, PaO_2/ FiO_2, pupillary reflexes, and the use of analgesics. In addition, the following rarely included predictors in the literature were included as they were deemed to be important in our survey: sex, height, ICU length of stay, lactate, presence of cardiac arrest with resuscitation in 24 hours prior to WLST and pulse rate. After the assessments of correlation and distribution of the 22 potential predictors, they were narrowed down to 13 potential predictors for inclusion in our *classical* models. Correlation matrices using both parametric measure, Pearson correlation, and non-parametric measure, Spearman-rank correlation, were employed due to the presence of continuous and categorical data (for plots, refer APPENDIX 4a, 4b). Among pairs of substantially correlated ($\geq$0.6) potential predictors, the ones with more complete data were preferred. The 13 potential

predictors satisfied the traditionally applied rule of thumb of a predictor per 10 events for multivariable logistic regression analysis. These included admission diagnosis, comorbidities, BMI, APACHE II score, event of cardiac arrest resuscitated in the 24 hours preceding WLST, vasopressor use, use of opioid analgesics, GCS score at WLST, pupillary reflex, ventilation support mode, PaO2/ FiO2, and respiratory rate.

For all the 22 the potential predictors, missing data was imputed using a multivariate imputation by chained equations (MICE) by random forest algorithm. The R-package *mice* (van Buuren, et al., 2018) was used to perform the imputation. Multivariate imputation by chained equations doesn't impose a common probability distribution across the dataset and assumes that each variable can have a unique probability distribution. The MICE algorithm can be used with any modeling approach, like random forest, thus allowing for the inclusion of nonlinear relationships among the variables when developing imputations. In this method, imputations would be taken as random draws from those in the same terminal node as the individual with missing data. Studies have found MICE with random forest modeling approach to be associated with more accurate estimates than MICE alone (Finch, Finch, & Singh, 2016) (Shah, Bartlett, Carpenter, Nicholas, & Hemingway, 2014). Imputed dataset was used to develop models. In this study, a stochastic single imputation dataset was considered for further analysis. This is the default first of a series of multiple imputation datasets. This was considered after taking precautions of including potential predictor for which data is expected to be available in future and included potential predictors containing fewer missing values in current dataset. A single imputation dataset is easier to work with in the absence of having to bother with the combination of results over different multiple imputation datasets and the disadvantages are considered less

relevant with relatively few missing values, and in datasets with greater than 100 events (Steyerberg, 2009).

In order to model the potential predictors, it was decided to put them into groups in order to create a model that was clinically meaningful for future knowledge users. Among these, the following potential predictors were categorical: cardiac arrest with resuscitation in the one hour prior to initiation of withdrawal of therapy present (or not), comorbidities (none, cardio-respiratory or others), ICU admission diagnosis (medical, non-traumatic brain injury neurological, surgery, and traumatic brain injury); vasopressor administered (or not), opioid analgesic administered (or not) at one-hour pre-withdrawal initiation; presence (or absence) of spontaneous breathing, and pupillary reflex present (or not). For the analysis, continuous potential predictors that were categorised, included: BMI categorised as below and above 30 kg/m2; APACHE II score as less than 15, 15-25 and greater than 25; respiratory rate as below 12 breaths/ minute, 12 -25 breaths/minute, and greater than 25 breaths/ minute; systolic blood pressure as above and below 100 mm Hg; , PaO2 to F iO2 ratio as below 100, 100-200 and above 200; GCS as above and below 3. Predictors of age; height; and ICU stay duration, pulse rate, lactate levels, and arterial pH levels at the initiation of WLST were included as continuous variables. Descriptive analyses were repeated using means ± standard deviation or median and interquartile range or proportions for the study population.

4.5.c. Model development

4.5.c.i. The *classical* prediction model

[Multivariable logistic regression model developed using *a priori* selected potential predictors]

The selected 13, out of the pool of 22, *a priori* selected potential predictors were used to develop a multivariable logistic regression analysis. All potential predictors were retained in the model and no selection technique (backwards or forwards) was employed. In view of a sample size of 307 patients and 177 outcome events, the complete dataset was used toward model development, followed with a rigorous bootstrap internal validation. This model was referred to as our *classical* model developed with *a priori* selected potential predictors.

Assessment of model prediction performance

Model performance was assessed by examining the following model discrimination indices: area under the receiver operating characteristic curve, sensitivity, specificity, positive and negative predictive values. Sensitivity is the true positive rate and estimates the proportion of correctly predicted actual positives. Specificity is the true negative rate that estimates the proportion of correctly predicted true negatives. Positive predictive value (PPV) measures the proportion of true positives among the predicted positives. Similarly, negative predictive value (NPV) measures the proportion of true negatives among the predicted negatives. While sensitivity and specificity reflect the discriminative performance of the model, the PPV and NPV values would depend on the prevalence of the outcome event in the underlying population. Overall accuracy is the rate of correctly predicted positives and negatives in the sample. Area under the curve (AUC) of the plot of true positive rates against false positive rates is a measure of discrimination. It is also referred to as the c-index. The AUC is the measure of the

concordance of predictions with actual outcomes. Ninety-five percent confidence interval (CI) were calculated using the *pROC* package (Robin, et al., 2018) . The package computes the confidence interval (CI) of the coordinates of a ROC curve and by default, the 95% CI are computed with 2000 stratified bootstrap replicates. Sensitivity, specificity, NPV and PPV values were reported based on assessed best thresholds. In the case of multiple best thresholds, the assessment selects a best threshold at random. Overall goodness-of-fit was evaluated using Brier score. Brier score is the mean squared error between outcome and prediction and informs model calibration through a combination of reliability, resolution, and uncertainty.

Validation of model's prediction performance

Internal validation via Bootstrap was performed to calculate optimism adjusted calibration indices for the model, using the *rms* package (Harrell Jr, 2018). Bootstrapping is the most efficient validation procedure since it does not involve holding out any data, allowing for revalidation of all aspects of model development on samples taken with replacement from the whole sample. The results from internal validation were presented in a tabular form (TABLE 8). The first row, original, contained the values from the model fitted and evaluated in the original study data used to develop it. The second row, training-set, contained the mean (across the bootstrap samples) values from the model fitted to the bootstrapped dataset when evaluated in the bootstrapped dataset. The third row, test-set, contained the mean values from model fitted to the bootstrap datasets when evaluated in the original study dataset. The difference between corresponding values from these two latter rows represented the estimated optimism. The fourth row contained the optimism adjusted values. Values reported in the table comprised of the Nagelkerke's R^2 values and the values of the indices from the calibration curves for the

respective rows. The Nagelkerke's R^2, that is the Nagelkerke-Cox-Snell-Maddala-Magee R^2 index, was calculated as an approximation of proportion of variance in the outcome associated with the predictors. For logistic regression models, it is not possible to compute a single R^2 statistic akin to the R^2 in the linear regression models. There are pseudo-R^2s, like the Nagelkerke's R^2, that have been proposed but these cannot be interpreted independently or compared across datasets. They are valid and useful in evaluating multiple models developed to predict the same outcome in the same dataset. Pseudo R^2 statistic calculated would be used to compare on the same data, predicting the same outcome. In this situation, the higher pseudo R^2 indicates which model better predicts the outcome. The indices of unreliability (lack of calibration), U, discrimination, D, over-all quality, Q, and the maximum absolute difference in predicted and loess-calibrated probabilities, E_{max}, were obtained from the calibration equations for the respective rows. A calibration curve is a scatter plot of the observed outcome frequencies vs. the predicted probabilities from the model. In models with binary outcome, like those developed in this study, the y-axis of the plot contains values of only 0 and 1. This requires the use of a smoothing technique, e.g. loess non-parametric smoothing, to estimate the observed probabilities of the outcome in relation to the predicted probabilities. The values for intercept and slope are informative of prediction accuracy of the model. The intercept provides an estimate of systematically too high/low predicted probabilities while the slope provides estimates of extremeness of predicted probabilities. When the calibration curve is linear, perfect predictions should be on the 45° line indicated by a slope of. Indices of unreliability (lack of calibration), U, discrimination, D, and over-all quality, Q, were obtained from the calibration equation. These measures are derived from the likelihood ratio tests of the equation. The overall quality index, Q,

is a logarithmic scoring rule and calculated as the difference between the discrimination and unreliability indices.

4.5.c.ii. The new *classical* model

[Multivariable logistic regression model developed using *a priori* selected and physician's prediction as potential predictors]

In a sensitivity analysis, the new *classical* model was developed as the re-analyzed *classical* multivariable logistic regression model with physician's prediction included as an additional predictor. Prediction performance of the new *classical* model was assessed similarly as discussed in the case of *classical* model. However, when comparing models based on AUC, DeLong et.al. point out that the AUCs of models developed from the same dataset are not independent but, rather correlated (DeLong, DeLong, & Clarke-Pearson, 1988). The authors recommend calculation of 95% CI to assess the significance of the observed apparent difference in the AUCs. The authors caution against drawing conclusions of superiority of a model based on a direct comparison of their AUCs. Accordingly, in the current study, while the performance indices are presented side-by-side, the differences in the AUCs have not been assessed for significance. As a result, apparent differences in AUC are reported as such and interpreted with caution as apparent superiority/ inferiority and not as conclusive superiority/ inferiority of a model.

4.5.c.iii. The *ensemble* prediction model

[Random forest classification developed using *a priori* selected potential predictors]

A model was developed using an 'ensemble' random forest classification approach with all 22 *a priori* predictors included. R-package *randomForest* was used for this analysis

(Breiman, Cutler, Liaw, & Wiener, 2018). The dataset was divided in a ratio of 70:30 to create a training and a testing set respectively. The first model was developed using 2000 trees and default *mtry* (*mtry* =√p, where p is the number of predictors). The value of *mtry* indicated the random number of predictors the model examines to select the one best predictor to split the data at a node. A tuned model was developed using optimum number of trees that minimize the *out-of-bag* error (misclassification error) from a plot of number of trees vs *out-of-bag* error. The optimal *mtry* was selected by examining a plot of *out-of-bag* error vs *mtry* and locating the number of potential predictors that minimized the *out-of-bag* error rate for the optimum number of trees identified. This model was referred to as our *ensemble* model developed with *a priori* selected potential predictors. In order to identify individual predictors important to the model, 2 plots were obtained using 2 different criteria respectively, showing the 10 predictors that contributed most to model accuracy. In one visual representation, predictors were plotted on the y-axis against the decrease in accuracy in their absence as plotted on the x-axis. In the second visual representation, predictors were plotted on the y-axis against decrease in the Gini coefficient in their absence as plotted on the x-axis. Variables that result in nodes with higher purity have a higher decrease in Gini coefficient when excluded.

Assessment of model prediction performance

Model performance was assessed by examining the following model discrimination indices: area under the receiver operating characteristic curve, overall accuracy, sensitivity, specificity, PPV and NPV. The *caret* package was used for this (Kuhn, 2018). Overall goodness-of-fit was evaluated using Brier score.

Validation of model's prediction performance

The random forest approach relies on bootstrapping, bagging (bootstrap aggregating) and cross-validation techniques to train and test an algorithm. Values from the model's performance in the test-set dataset were used for comparison of the model's prediction performance. A separate bootstrap cross-validation assessment was performed with 99 iterations using the final tuned model parameters. The R-package *rfUtilities* was used for this (Evans & Murphy, 2018). Performance in the cross-validation set is reported in addition to test-set performance reported from the random forest model.

4.5.c.iv. The new *ensemble* prediction model

[Random forest classification developed using *a priori* selected potential predictors]

The new *ensemble* model was the re-analyzed *ensemble* random forest classification model with physician's prediction now included as an additional predictor. The prediction performance of the new *ensemble* model was similarly assessed as discussed in the case of the *ensemble* model above.

4.5.c.v. The *univariable* model

This model was developed using the logistic regression approach, with the physician's prediction as the predictor of outcome. This *univariable* model performance was assessed similarly as discussed in the case of the *classical* models.

CHAPTER 5. RESULTS

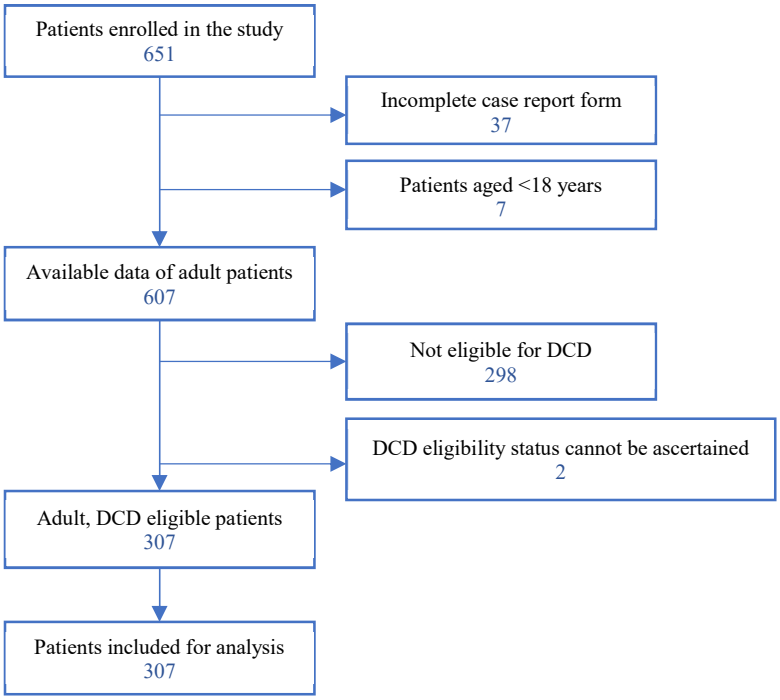
5.1. The data-set

5.1.a. Description of the study sample

Six hundred and fifty-one patients were enrolled between April 2015 and July 2018. The patients were enrolled from 19 mixed medical-surgical,university affiliated, ICUs from 3 different countries. Patients were enrolled trhough 15 centers across Canada, 3 centers in the Czech Republic and one center in the Netherlands. Out the 651 patients enrolled, 607 completed case report forms were available for adult, DCD eligible patients, in whom the decision to withdraw life-sustaining therapy had been made. Among these 607 patients, 50.6 % satisfied DCD eligibility criteria and constituted the final study population of 307 DCD eligible, adult patients (FIGURE 6).

The average age of the study population was 61 with males making up the majority of the cohort (61.9%) (TABLE 5). Almost half of the final population had a form of brain injury (traumatic and non-traumatic) with the remainder being mostly medical admissions. As a result, the mean Glasgow Coma Scale of 4.3 indicated a population with severe neurological deficit prior to WLST. Cardio-respiratory conditions were the most commonly reported comorbidity (34.9%) and a cardiac arrest requiring resuscitation in the 24-hours leading to WLST was documented in 15.3% of the population. A majority of the population was dependent on controlled mechanical ventilation support (68.7%) and more than a third (37.8%) required vasopressors. Correspondingly, the cohort had a high APACHE II (26.3) score indicating an elevated severity of illness.

FIGURE 6: Schematic overview of the population included in the study



The median duration of time to death for the whole cohort was 1.36 hours and the outcome of cardio-circulatory death within 120 minutes of WLST was observed in 177 (57.7%) of the included patients.

5.1.b. Completeness of data

Complete data was available for the potential predictors of age, sex, admission diagnosis, cardiac arrest with resuscitation within 24 hours prior to WLST, ICU length of stay, vasopressor and analgesic use and APACHE II score at WLST (TABLE 5). Among candidate predictors with missing data, the proportion of missing data ranged from 0.7%, for pupillary reflex and respiratory rate at WLST, to 92.8% for oculovestibular reflex.

Table 5: Characteristic of study population

Patient characteristics	N=307	Patients with missing data [n (%)]
On admission to ICU		
Age in years [Median (Q1 - Q3)]	61.1 (50.5 - 68.6)	0
Sex [n (%)]		0
Female	117 (38.1%)	
Male	190 (61.9%)	
Height in cm [Mean ± Standard Deviation]	171.9 ± 13.2	33 (10.7%)
Admission Diagnosis [n (%)]		0
Medical	131 (42.7%)	
Non-traumatic brain injury Neurological	108 (35.2%)	
Surgery (Non-traumatic brain injury)	15 (4.9%)	
Traumatic brain injury	53 (17.3%)	
Comorbidities [n (%)]		23 (7.5%)
None	82 (26.7%)	
Other	95 (30.9%)	
Cardio-respiratory	107 (34.9%)	
CT-Scan-Head [n (%)]		165 (53.7%)
Infection/ tumor	6 (2.0%)	
Cerebral edema	33 (10.7%)	
Hematoma/ haemorrhage	103 (33.6%)	
BMI in kg/m^2 [Mean ± Standard Deviation]	30.1 ± 16.7	33 (10.7%)
APACHE II Score [Mean ± Standard Deviation]	26.3 ± 8.6	0
ICU stay duration in hours [Median (Q1 - Q3)]	[95.12 (46.13 – 175.31)]	0
At one hour prior to-WLST		
Cardiac arrest with resuscitation within 24 hours pre- WLST [n (%)]		0
Yes	47 (15.3%)	
No	260 (84.7%)	
Opioid analgesic use one-hour pre-WLST [n (%)]		0
Yes	58 (18.9%)	
No	249(81.1%)	
Vasopressor use one-hour pre-WLST [n (%)]		0
Yes	116 (37.8%)	
No	191 (62.2%)	
GCS score [Mean ± Standard Deviation]	4.3 ± 2.1	6 (2.0%)

Patient characteristics	N=307	Patients with missing data [n (%)]
Lactate in mmol/L [Mean ± Standard Deviation]	3.2 ± 5.3	19 (6.2%)
pH [Mean ± Standard Deviation]	7.4 ± 0.1	16 (5.2%)
PaO2/ FiO2 ratio [Mean ± Standard Deviation]	254.3 ± 111.9	22 (7.1%)
PaO2 [Mean ± Standard Deviation]	112.5 ± 52.0	16 (5.2%)
FiO2 [Mean ± Standard Deviation]	49.8 ± 25.3	16 (5.2%)
Pulse rate as rate per minute [Mean ± Standard Deviation]	91.8 ± 23.5	2 (0.7%)
Systolic blood pressure in mm Hg [Mean ± Standard Deviation]	126.7 ± 58.9	4 (1.3%)
Respiratory rate as breaths/ minute [Mean ± Standard Deviation]	19.7 ± 8.1	2 (0.7%)
Spontaneous respiration [n (%)]		72 (23%)
Yes	24 (7.8%)	
No	211 (68.7%)	
Pupils [n (%)]		10 (3.3%)
Yes	207 (67.4%)	
No	90 (29.3%)	
Cough [n (%)]		53 (17.3%)
Yes	180(58.6%)	
No	74 (24.1%)	
Gag [n (%)]		88 (28.7%)
Yes	116 (37.8%)	
No	103 (33.6%)	
Corneal [n (%)]		154 (50.2%)
Yes	92 (30.0%)	
No	61 (19.9%)	
Oculovestibular [n (%)]		285 (92.8%)
Yes	11 (3.6%)	
No	11 (3.6%)	
Oculocephalic [n (%)]		261 (85.0%)
Yes	27 (8.8%)	
No	19 (6.2%)	

BMI = body mass index;
CT = computed tomography;
FiO2 = fraction of inspired oxygen;
GCS = Glasgow coma scale
ICU = intensive care unit
n (%) = count (proportion out of 307 as %)
PaO2 = partial pressure arterial oxygen;
Q1 = first quartile
Q3 = third quartile
WLST = withdrawal of life-sustaining therapy

5.2. Developing prediction models

5.2.a. Model 1: The *classical* model

[Multivariable logistic regression model developed using *a priori* selected potential predictors]

The 13 potential predictors included in this model are listed in TABLE 6. The Glasgow Coma Score and systolic blood pressure emerged as significant independent predictors for death within 120 minutes of WLST (TABLE 6). Patients with a GCS score of 3 (the lowest possible) and those with a systolic blood pressure lower than 100 mm Hg were twice as likely to die within 120 minutes of WLST [odds ratio (OR) of 2.20 and 2.01, respectively].

The model's discrimination performance was assessed, and the ROC curve was plotted (for plot of ROC curve refer APPENDIX 5) and the 95% confidence intervals were estimated (TABLE 7). The original model demonstrated an accuracy rate of 68.4 % (95 % CI: 62.5 %, 73.6 %) implying that in 95 % of these assessments, the model correctly predicted the outcomes between 62.5 % and 73.6% in the resamples. Among other measures of model discrimination, model sensitivity was 62.7 % (95 % CI: 45.8 %, 80.8). The model's specificity was 76.9 % (95 % CI: 56.2 %, 90.8 %). The PPV was 78.3 % (95 % CI: 70.3 %, 88.0 %) and NPV was 60.1 % (95 % CI: 53.6 %, 70.5 %). The AUC, also referred to as the C-index, was 0.73 (95 % CI: 0.67, 0.79).

TABLE 6: The *classical* multivariable logistic regression model with *a priori* selected potential predictors

Patient characteristics	Odds Ratio (95% CI)
On admission to ICU	
Admission Diagnosis (ref: Traumatic brain injury)	
Non-traumatic brain injury neurological	1.02 (0.47, 2.22)
Surgery (non-traumatic brain injury)	0.90 (0.24, 3.28)
Medical	0.96 (0.43, 2.12)
Comorbidities (ref: None)	
Other	0.74 (0.38, 1.45)
Cardio-respiratory	0.53 (0.27, 1.01)
BMI (kg/m2) [≥30 vs <30]	1.60 (0.90, 2.82)
APACHE II Score [ref: Score <15]	
Score 15-24	0.84 (0.27, 2.64)
Score ≤25	1.20 (0.38, 3.75)
One hour prior to WLST	
Cardiac arrest with resuscitation within 24 hours pre-WLST [Yes vs No]	0.52 (0.24, 1.13)
Opioid analgesic use 1-hour pre-WLST [Yes vs No]	1.26 (0.66, 2.42)
Vasopressor use 1-hour pre-WLST [Yes vs No]	1.46 (0.84, 2.56)
GCS score [3 vs >3]	**2.20 (1.25, 3.86) ***
PaO2 to FiO2 ratio [ref: ≤100]	
PaO2 to FiO2 ratio 101-200	0.85 (0.28, 2.57)
PaO2 to FiO2 ratio > 200	0.41 (0.14, 1.18)
Systolic blood pressure less then 100 mm Hg [ref >100 mm Hg]	**2.01 (1.10, 3.70) ***
Respiratory rate (breaths/ minute) [ref: <12]	
Respiratory rate 12-25	0.70 (0.30, 1.66)
Respiratory rate >25	1.07 (0.39, 2.96)
Spontaneous respiration [Yes vs No]	0.59 (0.23, 1.51)
Pupillary reflex [Yes vs No]	0.63 (0.34, 1.15)

BMI = body mass index;
CI = confidence interval
FiO2 = fraction of inspired oxygen;
GCS = Glasgow coma scale
ICU = intensive care unit
OR = odds ratio
PaO2 = partial pressure arterial oxygen;
WLST = withdrawal of life-sustaining therapy

TABLE 7: Evaluation of the *classical* model

Physicians prediction	Values from the original model †	Optimism adjusted values *
Accuracy	68.4 % (62.5 % - 73.6 %)	
Sensitivity	62.7 % (45.8 % - 80.8 %)	
Specificity	76.9 % (56.2 % - 90.8 %)	
PPV	78.3 % (70.3 % - 88.0 %)	
NPV	60.1 % (53.6 % - 70.5 %)	
AUC	0.730 (0.674 - 0.786)	0.66
Brier Score	0.207	0.235

The classical model is the multivariable logistic regression model developed using a priori selected potential predictor

†Values are from best threshold in 2000 bootstrap resamples
** Bootstrap validation over 200 resamples*

A bootstrap validation assessment was performed using 200 resamples. During the validation, the model's AUC in the training-set was 0.76 compared to the AUC of the original model (AUC = 0.73). The model's AUC in the test set was lower compared to the original model AUC. The overall optimism adjusted AUC was 0.66 (TABLE 8). The optimism adjusted AUC observed was much lower compared to the original model AUC.

TABLE 8: Performance indices from bootstrap validation of the *classical* model

Models	R^2	Intercept	Slope	E_{max}	U	Q	AUC	B
Original	0.210	0	1	0	-0.007	0.174	0.730	0.207
Training- set	0.274	0	1	0	-0.007	0.232	0.764	0.193
Test-set	0.153	0.082	0.664	0.106	0.027	0.090	0.696	0.222
Adjusted	0.089	0.082	0.664	0.106	0.027	0.032	0.661	0.235

The classical model is the multivariable logistic regression mode developed with predictors selected a priori
AUC=area under the curve; calculated from Somers's Dxy as [(1+ Dxy)/2]
B= Brier score
E_{max}= the maximum absolute difference in predicted and calibrated probabilities
Q= overall quality index (logarithmic probability score); calculated as (D – U), where D is the discrimination index given by (model L.R. ($\chi 2 - 1$)/n)
R^2= Nagelkerke's R^2
U= the unreliability index, calculated: difference in -2 log likelihood between un-calibrated Xβ and Xβ with overall intercept and slope calibrated to test sample / n

The model's goodness-of-fit assessed through the Brier score was 0.21 with an optimism adjusted Brier score of 0.24 (TABLE8). Brier score values range between 0 and 1, where 0 indicates best predictions with total accuracy and 1 indicates completely inaccurate predictions. Lower Brier scores for a set of predictions, indicate better calibration.

Other calibration indices for the *classical* model were assessed during model validation and are as reported in TABLE 8. The intercept and slope of the calibration curve for the adjusted model was 0.08 and 0.66 respectively. A curve along the 45° line would have the values of 0 and 1 for intercept and slope respectively. Closeness of a calibration curve to a 45° line demonstrates validation on an absolute probability scale. The calibration curve captures the correspondence of average outcomes and average predictions indicating the apparent calibration of the prediction model. The optimism adjusted E_{max} for the model was 0.11. An index of unreliability (lack of calibration), the E_{max} is the maximum absolute difference in predicted and loess-calibrated probabilities. It ranges between 0 and 1 and lower E_{max} is preferable. The optimism adjusted unreliability index was assessed to be 0.03. For the unreliability index U, values close to zero or less than zero are desirable for a reliable model. Values less than 0 indicates better reliability than expected by chance. Values below 0.05 indicate that model is reliable for most part. The, adjusted Q was 0.03. The overall quality index Q, is the difference between discrimination and unreliability. A negative Q suggests poor discrimination that is unable to overcome serious unreliability. The optimism adjusted Nagelkerke's R^2 was 0.09. The Nagelkerke's R^2 is suggestive of the approximate proportion of variance in the dependent variable associated with the predictor (independent) variable. Values range between 0 and 1, where larger R^2 values

indicate that more of the variation is explained by the model. It should be noted that the Nagelkerke's R^2 is not an exact counterpart of the R^2 from a linear regression model.

5.2.b. Model 2: The *ensemble* model

[Random forest classification model developed using *a priori* selected potential predictors]

The complete list of 22 *a priori* selected potential predictors was used in the random forest classification model (APPENDIX 6). A post-hoc analysis was performed using these potential predictors to assess their univariable association with the outcome and is discussed further on. The tuned *ensemble* model algorithm was developed using 680 trees and a *mtry* of 4. These were selected using the out of bag error rate plots included in APPENDICES 7 and 8. The tuned model, when assessed in the test-set, demonstrated an overall accuracy of 64.6 %, sensitivity of 78 %, specificity of 43.2 %, PPV of 68.7 % and NPV of 55.2 % (TABLE 9). The AUC was 0.67 in training-set (for ROC plot refer APPENDIX 9) vs 0.64 in the test-set (for ROC plot refer APPENDIX 10). The model's test-set Brier score was 0.35. The tuned *ensemble* model was assessed through bootstrapped cross-validation. The cross-validation model performance was as follows: accuracy 64.8 %, sensitivity 60 %, specificity71.4 %, PPV 75 % and NPV 50 % (TABLE 9).

By calculating the change in the accuracy and Gini coefficients the following emerged as the most important predictors: age, height, ICU admission diagnosis, ICU length of stay, FiO2, lactate, blood pressure, PaO2/ FiO2 ratio, GCS score, pH, pulse rate, respiratory rate, PaO2, and

vasopressor use (FIGURE 7). The plots of the most important predictors from the *ensemble* model is presented in the FIGURE 7.

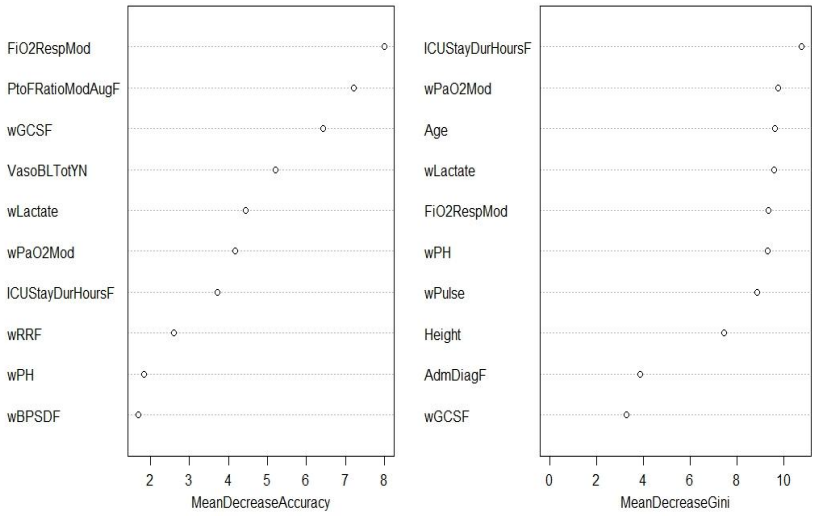
TABLE 9: Evaluation of the performance of the *ensemble* model

Performance index	Model 2: *Ensemble* (*a priori*) **	Model 2 CV*: Ensemble* (*a priori*) ***
Brier Score	0.35	-
AUC	0.644	-
Accuracy	64.6%	64.8%
Sensitivity	78.0%	60.0%
Specificity	43.2%	71.4%
PPV	68.7%	75.0%
NPV	55.2%	50.0%

The ensemble model is the random forest classification model developed using a priori selected potential predictors

Accuracy= correct predictions/ total
AUC= area under receiver operating characteristic curve
CI= confidence interval
NPV= negative predictive value
PPV= positive predictive value
*** values from random forest approach model performance in the test-set*
****CV= cross-validation over 99 iterations; values from cross-validation- set*

FIGURE 7: Importance of predictors from the *ensemble* model



The ensemble model is the random forest classification model developed using a priori selected potential predictors

The predictors on the y-axis appear in the order of importance, starting with the most important as reflected in corresponding values of their impact on the x-axis for the two criteria. The most important predictor causes the largest mean decrease in the accuracy category. Similarly, the most important predictor causes the largest mean decrease in the category of Gini coefficient.

5.2.c. Model 3: the *univariable* model

[Univariable logistic regression model developed using physician's prediction of outcome as the predictor]

Physician's predictions were not available in 39 study patients. Physician's prediction was found to be a significant predictor of death within 120 minutes of WLST in a univariable logistic regression analysis (APPENDIX 6). Patients predicted to die within this period were found to be 7 times as likely to die within 120 minutes of WLST with an OR of 6.98 (95 % CI: 4.18, 11.67). The original model AUC was 0.74 (95 % CI: 0.672, 0.776) as presented in TABLE 9. The ROC plot is included in appendix 11. The original model's accuracy was 73.0 % (95 % CI: 68.0 %, 77.7 %). The *univariable* model demonstrated good sensitivity, specificity, PPV and

NPV. The Brier score was 0.19 for this *univariable* model. Following the bootstrap validation assessment, the optimism adjusted AUC and Brier score were 0.75 and 0.19 respectively (TABLE 9). The model did not adjust for physician's experience or years of practice. Model calibration indices are presented in TABLE 10.

TABLE 9: Evaluation of the *univariable* model

Physicians prediction	Values from the original model †	Optimism adjusted values *
Accuracy	73.0 % (68.0 % - 77.7 %)	
Sensitivity	76.0 % (69.70% - 81.7 %)	
Specificity	68.8 % (60.8 % - 76.8 %)	
PPV	77.4 % (72.6 % - 82.1 %)	
NPV	67.2 % (61.0 % - 73.3 %)	
AUC	0.724 (0.672 – 0.776)	0.747
Brier Score	0.186	0.187

The univariable model is the univariable logistic regression model with physician's prediction as the predictor

†Values are from best threshold in 2000 bootstrap resamples
** Bootstrap validation over 200 resamples*

TABLE 10: Performance indices from bootstrap validation of the *univariable* model

Models	R^2	Intercept	Slope	E_{max}	U	Q	AUC	Brier score
Original	0.249	0	1	0	-0.007	0.208	0.724	0.195
Training-set	0.251	0	1	0	-0.007	0.211	0.724	0.193
Test-set	0.249	-0.019	1.011	0.006	0.001	0.201	0.724	0.196
Adjusted	0.247	-0.019	1.011	0.006	0.001	0.198	0.724	0.198

The univariable model is the univariable logistic regression model with physician's prediction as the predictor

AUC=area under the curve; calculated from Somers's Dxy as [(1+ Dxy)/2]
B= Brier score
E_{max}= the maximum absolute difference in predicted and calibrated probabilities
Q= overall quality index (logarithmic probability score); calculated as (D – U), where D is the discrimination index given by (model L.R. (χ2 − 1)/n)
R^2= Nagelkerke's R^2
U= the unreliability index, calculated: difference in -2 log likelihood between un-calibrated Xβ and Xβ with overall intercept and slope calibrated to test sample / n

5.3.a. Model 4: The new *classical* model

[Multivariable logistic regression model developed using *a priori* selected and physician's prediction potential predictors]

The *classical* approach model was re-analysed with the inclusion of physician's prediction along with the *a priori* potential predictors. Physician's prediction continued to be a significant predictor. Glasgow coma scale score continued to be a significant predictor in the new *classical* model, while comorbidities emerged as a significant predictor replacing systolic blood pressure. Patients with a prediction of positive outcome from physician were found to be seven times as likely to die within 120 minutes of WLST (OR 7.21; CI: 3.89, 13.38). Patients with a cardio-respiratory comorbidity were less likely and those with very low level of consciousness, lowest GCS score of 3, were assessed to be twice as likely to die within 120 minutes of WLST (TABLE 11).

TABLE 11: The new *classical* model

Potential predictors	Odds Ratio (95% CI)
At admission	
Admission Diagnosis (ref: Traumatic brain injury)	
Non-traumatic brain injury neurological	0.9 (0.38, 2.14)
Surgery (non-traumatic brain injury)	1.09 (0.26, 4.58)
Medical	1.01 (0.42, 2.46)
Comorbidities (ref: Cardio-respiratory)	
Other	1.49 (0.74, 3.00)
None	**2.11 (1.01, 4.39) ***
BMI (kg/m2) [≥30 vs <30]	1.78 (0.95, 3.33)
APACHE II Score [ref: Score <15]	
Score 15-24	0.53 (0.15, 1.81)
Score ≤25	0.06 (0.17, 2.08)
At one-hour pre-WLST	
Cardiac arrest with resuscitation in 24 hours pre-WLST [Yes vs No]	0.98 (0.40, 2.38)
Vasopressor use 1-hour pre-WLST [Yes vs No]	0.98 (0.52 1.86)
Systolic blood pressure (mm Hg) [>100 vs ≤ 100]	0.64 (0.32, 0.28)
Opioid analgesic use 1-hour pre-WLST [Yes vs No]	1.65 (0.80, 3.43)
GCS score [3 vs >3]	**2.37 (1.26, 4.45) ***
Pupillary reflex [Yes vs No]	0.63 (0.2, 1.27)
PaO2 to FiO2 ratio [ref: ≤100]	
PaO2 to FiO2 ratio 101-200	0.98 (0.28, 3.40)
PaO2 to FiO2 ratio >200	0.43 (0.13, 1.38)
Respiratory rate (breaths/ minute) [ref: <12]	
Respiratory rate 12-25	0.63 (0.23, 1.71)
Respiratory rate >25	0.77 (0.24, 2.47)
Spontaneous respiration [Yes vs No]	0.93 (0.32, 2.71)
Physician's Prediction [Yes vs No]	**7.21 (3.89, 13.38) ***

BMI = body mass index;
CI = confidence interval
FiO2 = fraction of inspired oxygen;
GCS = Glasgow coma scale
ICU = intensive care unit
OR = odds ratio
PaO2 = partial pressure arterial oxygen;
WLST = withdrawal of life-sustaining therapy

The new classical model is the multivariable logistic regression model with a priori selected and physician's prediction as potential predictors

The new *classical* approach original model AUC was 0.82 (95% CI: 0.774, 0.868). The plot of the ROC curve is included in appendix 12. The Brier score was 0.17 (TABLE 12). With the exception of PPV, the new model demonstrated better performance on all other indices. Optimism adjusted AUC was found to 0.77 and Brier score was 0.20 (TABLE 12). These were better when compared to adjusted AUC and Brier score from the *classical* model without the inclusion of physician's prediction (TABLE 12). The optimism adjusted values of the other indices of model calibration were also found to be indicative of improved performance (TABLE 13).

TABLE 12: Evaluation of the new *classical* model performance

***Classical* model (*a priori*)**	**Values from unadjusted model †**	**Optimism adjusted values ***
Accuracy	76.7 % (71.7 % - 81.3 %)	
Sensitivity	74.3 % (59.4 % - 84.0 %)	
Specificity	81.6 % (69.6 % - 92.8 %)	
PPV	84.8 % (78.5 % - 92.5%)	
NPV	68.9 % (61.1 % - 76.7 %)	
AUC	0.821 (0.774 – 0.868)	0.772
Brier Score	0.1712	0.198

The new classical model is the multivariable logistic regression model developed using a priori selected and physician's prediction as potential predictors

†Values from best threshold in 2000 bootstrap resamples
** Bootstrap validation over 200 resamples*

TABLE 13: Performance indices of the new c*lassical* model

Models	R^2	Intercept	Slope	E_{max}	U	Q	AUC	Brier Score
Original	0.377	0	1	0	-0.007	0.332	0.821	0.171
Training-set	0.434	0	1	0	-0.007	0.393	0.842	0.158
Test-set	0.318	0.039	0.758	0.068	0.021	0.245	0.793	0.186
Adjusted	0.261	0.039	0.758	0.068	0.021	0.184	0.772	0.198

The new classical model is the multivariable logistic regression model developed using a priori selected and physician's prediction as potential predictors

AUC=area under the curve; calculated from Somers's Dxy as [(1+ Dxy)/2]
B= Brier score
E_{max}= the maximum absolute difference in predicted and calibrated probabilities
Q= overall quality index (logarithmic probability score); calculated as (D – U), where D is the discrimination index given by (model L.R. (χ2 − 1)/n)
R^2= Nagelkerke's R^2
U= the unreliability index, calculated: difference in -2 log likelihood between un-calibrated Xβ and Xβ with overall intercept and slope calibrated to test sample / n

5.3.b. Model 5: The new *ensemble* model

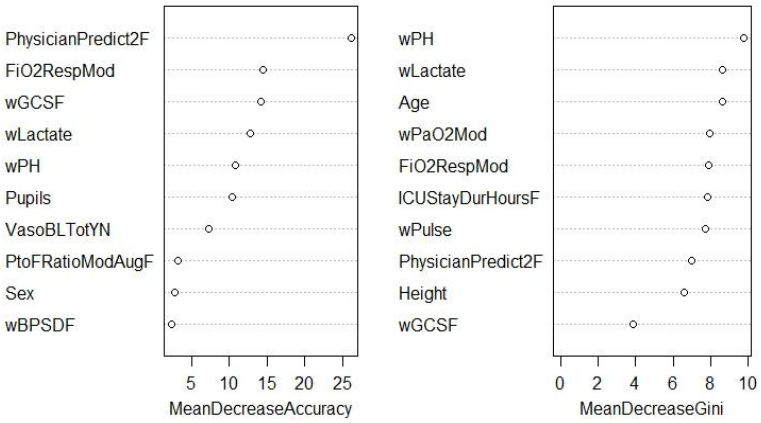
[Random forest classification model developed using *a priori* selected and physician's prediction as potential predictors]

The new *ensemble* model found physician's prediction to be one of the important predictors. New predictors emerging important in this assessment were sex and pre-WLST pupillary reflex replacing those of pre-WLST respiratory rate and admission diagnosis from the important predictors found in the earlier model (FIGURE 8).

When examining the performance of the new *ensemble* model with the inclusion of physician's prediction, it was found to be better in all performance indices assessed. The test-set AUC improved to 0.75 (for ROC plot refer to APPENDIX 14) compared to 0.64 in the earlier model. Goodness of fit assessment with Brier score also found the new *ensemble* model improved with a score of 0.277 compared to 0.354 in the test-set. In bootstrapped cross

validation, the addition of the new predictor did not improve performance. While accuracy, sensitivity, PPV and NPV remained at similar levels, there was reduction in specificity from 71.4% to 66.7% (TABLE 14).

FIGURE 8: Important predictors from the new *ensemble* model



The new ensemble model is the random forest classification model developed using a priori selected and physician's prediction as potential predictors

The predictors on the y-axis appear in the order of importance, starting with the most important as reflected in corresponding values of their impact on the x-axis for the two criteria. The most important predictor causes the largest mean decrease in the accuracy category. Similarly, the most important predictor causes the largest mean decrease in the category of Gini coefficient.

5.4. Comparison of the model performances

5.4.a. The *classical* model vs the *ensemble* model

The comparison of model performance of prediction of death within 120 minutes of WLST between the *classical* and the *ensemble* models are presented in TABLE 15. The models were comparable on AUC and accuracy with the *classical* model showing a slightly better AUC. Though the *ensemble* model showed better sensitivity, it's specificity was poor. Both PPV and

NPV were better in the case of the *classical* model. The *classical* model also had a better Brier score compared to the *ensemble* model. However, in cross validation the *ensemble* model showed comparable results for accuracy, sensitivity, specificity and PPV while, NPV was still found to be lacking.

5.3.b. The *classical* vs the *ensemble* vs the *univariable* models

Comparing the *classical*, the *ensemble* and the *univariable* models, the *univariable* model of physician's prediction of death within 120 minutes of WLST outperformed the other models with better Brier scores, AUC, accuracy, and NPV. However, the *ensemble* model showed best sensitivity, while the *classical* model showed the best specificity (TABLE 15).

TABLE 14: Comparison of model performance: the *classical* model vs the *ensemble* model

Performance index	Model 1: *Classical* (*a priori*) †	Model 2: *Ensemble* (*a priori*) **	Model 2 CV*: Ensemble* (*a priori*) ***
Brier Score	0.23*	0.35	-
AUC	0.680 *	0.644	-
Accuracy	68.4 %	64.6%	64.8%
Sensitivity	62.7 %	78.0%	60.0%
Specificity	76.9 %	43.2%	71.4%
PPV	78.3 %	68.7%	75.0%
NPV	60.4 %	55.2%	50.0%

Accuracy= correct predictions/ total
AUC= area under receiver operating characteristic curve
CI= confidence interval
NPV= negative predictive value
PPV= positive predictive value
** optimism adjusted values from bootstrap validation over 200 resamples*
*** values from random forest approach model performance in the test-set*
****CV= cross-validation over 99 iterations; values from cross-validation- set*
*†Values in Models 1 (except * are from best threshold in 2000 bootstrap resamples)*

TABLE 15: Comparison of model performance: the *classical* model vs the *ensemble* model vs the *univariable* model

Performance index	Model 1: *Classical* (*a priori*) †	Model 2: *Ensemble* (*a priori*) **	Model 2 CV*: Ensemble* (*a priori*) ***	Model 3: *Univariable* (Physician' s prediction) †
Brier Score	0.228*	0.35	-	0.187 *
AUC	0.680 *	0.644	-	0.747 *
Accuracy	68.4 %	64.6%	64.8%	73.0%
Sensitivity	62.7 %	78.0%	60.0%	76.0%
Specificity	76.9 %	43.2%	71.4%	68.8%
PPV	78.3 %	68.7%	75.0%	77.4%
NPV	60.4 %	55.2%	50.0%	67.2%

Accuracy= correct predictions/ total
AUC= area under receiver operating characteristic curve
CI= confidence interval
NPV= negative predictive value
PPV= positive predictive value
** optimism adjusted values from bootstrap validation over 200 resamples*
** *values from random forest approach model performance in the test-set*
****CV= cross-validation over 99 iterations; values from cross-validation- set*
*†Values in Models 1&3 (except * are from best threshold in 2000 bootstrap resamples)*

5.3.c. Comparing all five models

Overall, the inclusion of physician's prediction improved both *classical* and *ensemble* models as evident from comparison of performance of the corresponding new models in assessment categories presented in TABLE 16. The new *classical* model performed the best in most indices, while the new *ensemble* model had the best sensitivity. All models were comparable on PPV except for the *ensemble* model which showed the lowest value and the *classical* model showed the best performance. All models performed relatively poorly in NPV.

TABLE 16: Comparison of all five prediction models developed

Performance Index	Model 1: *Classical* (*a priori*) †	Model 4: new *Classical* (*a priori* + PP) †	Model 2: *Ensemble* (*a priori*) **	Model 5: New *Ensemble* (*a priori* + PP) **	CV Model2: *Ensemble* (*a priori*) ***	CV Model 5 : New *Ensemble* (*a priori* + PP) : ***	Model 3: *univariable* (Physician' s prediction) †
Brier Score	0.228*	0.198*	0.354	0.277	-	-	0.187 *
AUC	0.680 *	0.772*	0.644	0.753	-	-	0.747 *
Accuracy	68.4 %	76.7 %	64.60%	72.3%	64.8%	64.2%	73.0%
Sensitivity	62.7 %	74.3 %	78.0%	79.7%	60.0%	60.0%	76.0%
Specificity	76.9 %	81.6 %	43.20%	60.0%	71.4%	66.7%	68.8%
PPV	78.3 %	74.8 %	68.70%	77.0%	75.0%	75.0%	77.4%
NPV	60.4 %	68.9 %	55.20%	63.6%	50.0%	50.0%	67.2%

Accuracy= correct predictions/ total
AUC= area under receiver operating characteristic curve
CI= confidence interval
NPV= negative predictive value
PP= physician's prediction as a potential predictor
PPV= positive predictive value
** optimism adjusted values from bootstrap validation over 200 resamples*
** *values from random forest approach model performance in the test-set*
****CV= cross-validation over 99 iterations; values from cross-validation- set*
*†Values in Models 1,3&4 (except * are from best threshold in 2000 bootstrap resamples)*

5.5. Post-hoc analysis

Univariable analysis of the *a priori* selected potential predictors

The *a priori* potential predictors used in developing the models in this study were evaluated for their association with the outcome in univariable regression analysis after all the models were developed. The crude odds ratio and their corresponding distribution in the outcome categories have been presented in APPENDIX 6. Younger age, arterial acidosis, presence of increasing respiratory distress at WLST, lower systolic blood pressure of 100 mm Hg or less, lowest level of consciousness (GCS score of 3), rising lactate levels, increasing FiO2, absence of

pupillary reflex and vasopressor use were found to be independently associated with increased likelihood of death with 120 minutes of WLST (APPENDIX 6).

CHAPTER 6: DISCUSSION

6.1. Summary

The objective of our study was to develop a model to predict death within 120 minutes of WLST. A risk prediction tool to predict death would help to identify DCD eligible critically ill patients undergoing WLST for organ donation. Using *a priori* identified potential predictors, we developed two models based on two different statistical approaches: the *classical* multivariable logistic regression and the *ensemble* random forest classification. We also tested three other models using physician's prediction of death, alone and in conjunction with the two developed *a priori* models. We observed that 57.7% of our study population died within 120 minutes of WLST. The *classical* model demonstrated apparent overall better performance than the *ensemble* model with AUCs of 0.68 vs 0.64 respectively. The physician's prediction model performed better and appeared superior to the *a priori* models. The combination of the physician's prediction with the *a priori* models appeared to have best overall performance.

Comparing AUC and Brier score of the optimism adjusted c*lassical* model and the corresponding test-set values of the *ensemble* model, demonstrated that the *classical* model appeared to have better discrimination and goodness-of-fit. However, we noted that the observed optimism adjusted AUC of the *classical* model showed a large change from the model's original AUC. This would indicate presence of some overfitting, suggestive of *testimation* bias. Optimism adjustment informs overfitting and helps to estimate true performance of the model

when applied to the underlying population against apparent performance from estimates derived in the sample population. Overfitting is a major problem associated with regression modelling. This could arise either from model or from parameter uncertainties. Inclusion of predictors based on effect size, as determined through statistical testing, could contribute to model uncertainty. In some instances, certain predictors could have a relatively larger effect in certain sample populations and not in others. Overestimation of the effect of a predictor, or *testimation* bias, is difficult to avoid if predictor inclusion is based on only on instances of a relatively large effect sizes. In our study we relied on clinical expert opinion and existing evidence to pre-specify our potential predictors. We explicitly avoided exploring statistical effects of these predictors in the sample data prior to developing the models. We however undertook these assessments post-hoc to help compare our findings to existing prediction models in the literature. In linear prediction modeling another avenue of overestimation arises from the regression coefficients that are multiplied to the value of the predictors. Though the default estimation methods of the coefficients (maximum likelihood for logistic regression) are nearly unbiased, each coefficient is associated with some uncertainty which is reflected in the estimated standard error and 95% CI. This uncertainty leads to overestimation of predictions at the extremes of a linear predictor. While we avoided statistical predictor selection in order to minimise model overfitting and *testimation* bias, there were indications of overestimation suggested by the large optimism correction in AUC. This may have occurred due to the number of predictors used in the model. Our relatively small sample size could have also contributed since using a large sample size renders *testimation* bias, irrelevant.

A highly sensitive prediction model will maximise organs for transplantation, ensuring minimal loss of opportunity of making a transplantable organ available to those in need. Having good specificity, would enable the prediction model to also identify patients who would not die within the requisite time period for a transplantation which would help optimise healthcare resource utilization. If the prevalence of the outcome in is not known, PPV helps assess the proportion of patients who would die within 120 minutes out of all patients predicted to die within 120 minutes. A highly sensitive model is able to identify patients who would have the outcome, with high accuracy. Models with high sensitivity, specificity and corresponding PPV and NPV would ensure an efficient balance of identifying eligible donors, maximising organ transplantation while also minimizing lost opportunities of providing care arising from diverted resources. Between the two *a priori* models, for plausibly comparable accuracies the *ensemble* model had much better sensitivity. However, the goodness-of fit, Brier score, of the *ensemble* model was inferior to that of the *classical* model in our study sample.

Although the *classical* model appeared to perform better than the *ensemble* model, it is possible that in a larger cohort the random forest method may be more efficient and better performing. Healthcare datasets, often have smaller number of covariates compared to the sample size and focus on explanation and prediction (Shmueli, 2010). Logistic regression, a standard approach in this type of datasets, has been a commonly used statistical classification approach in medical literature among studies analysing binary outcomes (Shmueli, 2010). On the other hand, random forest classification algorithm is an emerging approach that focuses on prediction rather than explanation (Shmueli, 2010). This approach can handle highly correlated predictors, capture non-linear association patterns between predictors, perform excellently in

datasets where the number of predictors might be much larger than the number of observations or in cases of noisy datasets (Perlich, Provost, & Simonoff, 2003). The algorithm of random forest classification does not fit a model to the underlying data but, rather follows a decision tree approach, recursively partitioning the data into increasingly homogenous groups. The algorithm attempts to minimise loss of accuracy at these partitions. As a result, the algorithm is able to best utilize available predictors to arrive at the best classification even with changing datasets. If the dataset changes, the individual trees change. Being a combination of many trees, the overall forest remains rather stable. It is argued that logistic regression methods performs better for smaller datasets while random forest methods performs also reasonably well in smaller dataset while performing better in larger datasets (Perlich, Provost, & Simonoff, 2003) (Couronné, Probst, & Boulesteix, 2018). Perlich et. al. assessed classification accuracy, AUC, obtained by applying variants of logistic regression and random forest classification approaches to several large, binary-outcome data sets. The employed datasets ranged between one thousand examples to two million examples. The authors used learning curve to examine the relationship of the measures to the changes in the size of the dataset used to develop the classification models. Based on their findings, logistic regression models would not generally outperform random forest classification in all situations. This led the authors to suggest that logistic regression model performances might be better in smaller datasets while random forest classification may be better in larger datasets in general.

Perlich et al. further observed that tree-based probability estimation models, like random forest classification, often outperform logistic regression by producing probability-based rankings, especially for larger datasets. They found that the signal-to-noise separability of a

dataset could be a useful indicator of the approach more likely to be suitable. ‘Noise’ refers to meaningless information. Commonly, ‘noise’ could arise from erroneous measurements due to the measurement instrument or random errors arising from collection of erroneously documented information or introduced during data preparation processes. Some ‘noise’ in arguably unavoidable in real-world data (Zhu & Wu, 2004). According to the author’s findings, a random forest classification might be preferable for larger training-set sizes for which the classes can be separated well. On the other hand, a logistic regression approach might be preferable for smaller training-set sizes and where the classes cannot be separated well. The author’s findings suggest that the highly nonlinear nature of trees-based random forest approach might allow it to exploit structure when the signal separability is high. Therefore, we incorporated steps to control noise in the collected data to allow the models to demonstrate their ability to predict outcome in the current data-set. A non-interventional study design, as used in this study, would indicate that the quality of collected values of the predictors would depend on timely and correct documentation of these values and their availability for collection. The present study, being a study in critically ill patients, would suggest that collected data would be relatively less ‘noisy’ since progress is closely followed-up and well documented for individual patients. Coordinators were trained to ensure data quality and the prospective study design allowed collection of all information relevant to the study objective. During data processing, *a priori* rules were applied to categorise and clean data. Predictors found to be missing data for greater than a quarter of the study sample were not included as potential predictors. They might be missing information because these are either not assessed commonly in mixed ICUs or not assessed uniformly across all centers. As a result, even if such a predictor was a candidate for potential predictor, they were found to not

align with our study objective of using ordinarily employed assessments. These predictors were excluded from the *a priori* list of candidate potential predictors and consequently from current analysis.

It has been suggested that the assessment for the better model is multifaceted and requires a nuanced analysis (Box & Draper, 1987). Focusing on the AUC allows for the examination of probability ranking, not probability estimation. Logistic regression models are designed for probability estimation and might perform better in this department. Current thinking encourages examining learning curves for assessment of superior performance on particular set of predictors (Perlich, Provost, & Simonoff, 2003). Also, that comparisons from simple studies with one data-set size might not be appropriate to draw conclusions regarding the better modeling approach because one is better than the other for corresponding set of predictors or tasks. Perlich et. al. discuss the questionability of the practice of experimenting with smaller datasets (for efficiency reasons) commonly used to choose the best approach, and then "scaling up" the learning with the chosen approach. The apparent superiority of one method over another for one particular sample size may not necessarily carry over to larger samples (from the same *domain* or set of predictors). Keeping this in mind, we developed models using both the approaches of logistic regression and random forest classification to assess a suitable model in our current study sample. When these models are re-assessed in larger datasets, current findings will provide us a frame of reference to appreciate their strengths and suitability in the context of our target patient population (Couronné, Probst, & Boulesteix, 2018) (Perlich, Provost, & Simonoff, 2003). Evidence suggests caution in conclusions based on performance in certain training-set/test-set partitions (such as two-thirds/one-third) since this might not even generalize to the source dataset

(Perlich, Provost, & Simonoff, 2003). Assessing the models developed in the current study in a larger dataset, using learning curve analysis and performing sensitivity analysis using varying train-set/ test-set proportions would be necessary and to further assess the findings of model performance in our study. When comparing AUCs of models developed from the same dataset, we have refrained from concluding better or worse performance based on apparent differences of AUCs. Recalling the recommendation of DeLong et.al., significance of apparent differences might be commented on only in the presence of 95% CI of the observed difference (DeLong, DeLong, & Clarke-Pearson, 1988).

The current study is the first generalizable study to develop prediction models for post-WLST-time-to-death of 120 minutes in a cohort of DCD eligible, critically ill patients from mixed- ICUs across three different countries. Findings from this study will support future assessments towards identifying a final model that would be 'useful' for recommended clinical application. We assessed that favouring any one approach at the outset would require making many assumptions which might result in lost opportunities to arrive at a more efficient model. Based on current evidence in prediction modeling as discussed above, we decided to apply two different approaches with different known strengths. We believe that this will inform the final selection of a 'useful' model tailored to the peculiarities of the underlying population and prevalent objective assessment-measurements.

Our results demonstrated that physician's prediction was apparently superior in predicting death within 120 minutes of WLST than both our *a priori* models. Physician's prediction had higher AUC, sensitivity and PPV on direct comparison. There are multiple potential reasons that might be attributable to physicians being better at predicting death as

compared to the models. First, physicians may be utilizing predictors that were not captured in our dataset. Despite surveying experts in the field for important variables in predicting time to death, it's possible that there were some important predictors that we did not capture. Furthermore, the physicians may have had access to real-time data of the given predictors while our dataset only had a single snapshot. Physicians may also have been aware of the method of WLST to be applied which could have an impact on the time to death. As the physicians were often the ones performing the WLST this may have the effect of "a self-fulfilling prophecy". Finally, Physicians may have been aware of the patients' health trajectory while in the hospital and ICU and may have incorporated this information while estimating the probability of death.

While constructing our analysis plan, a decision was made to not include physician's prediction as a potential predictor in our initial models. Including physician's prediction could be a useful predictor informing accuracy with respect to the precise capture of certain predictors at decision time-point. As a result, we decided in favour of examining physician's prediction in a separate sensitivity analysis pursuing our primary aim of developing models that would inform prediction of the outcome of death within 120 minutes of WLST using commonly assessed objective measures. We attempted to include all important assessment parameters that experts would consider in predicting time to death by incorporating their feedback in deciding our list of *a priori* potential predictors before developing our models. However, there is a possibility that there might be one or more important predictors which may not be perceived as such though they influence physician's predictions.

The better model might be a subjective choice, based on a healthcare institution's resources and prevalence of the outcome in the patient population they serve. These estimates

would decide the optimum balance of sensitivity and specificity for that setting. In our study, the *a priori* models might be relatively comparable on AUC and accuracy. The *classical* model was more specific than sensitive while, the *ensemble* model was shown to be more sensitive. Though specificity was poor for the *ensemble* model in the test-set, in cross-validation it demonstrated an improvement in specificity. A conclusive assessment of these comparisons cannot be made in the absence of 95% CIs. The inclusion of physician's prediction as an additional predictor to the *a priori* models improved apparent performances of both models. While the optimism adjusted AUC of the new *classical* model and the test-set AUC of the new *ensemble* model might be relatively comparable, the new *classical* model had better accuracy between the two. The new *classical* model was more specific than sensitive while the new *ensemble* model was more sensitive than specific. The new *ensemble* model had the highest sensitivity while the new *classical* model had the highest specificity observed for any of the models developed in the current study. The goodness-of-fit was better in the case of the new *classical* model. However, the cross-validation performance of the new *ensemble* model appeared to be comparable to that of the earlier *ensemble* model. This might be indicative of the robust coping mechanism of the *ensemble* method and may indicate better generalisability to other datasets.

6.2. Comparison with other studies

6.2.a. Predictors

Glasgow coma score and systolic blood pressure emerged as independent predictors in the *classical* model. Age, height, ICU admission diagnosis, ICU length of stay, indices of oxygenation of FiO2, PaO2/ FiO2 ratio, respiratory rate and PaO2, arterial acidosis related predictors of lactate and pH levels, pulse and vasopressor use emerged as important predictors in

the *ensemble* model in addition to the 2 independent predictors found from the *classical* model. Out of these important predictors, age, height, ICU length of stay, respiratory rate, and admission diagnosis did not achieve statistical significance when analysed post-hoc using univariable analysis. If a statistical test of effect sizes had been applied for selecting potential predictors, as reported commonly in existing literature, these predictors might not have been included in the models developed. We found similar situations in the case of the new models developed with the addition of physician's prediction to the *a priori* ones. Comorbidities, found to be independent predictor of outcome in the new *classical* model, did not achieve statistical significance in the post-hoc univariable analysis. Also, sex, found to be among important predictors in the new *ensemble* model, did not show large effect-size in the post-hoc univariable analysis.

In previous studies, predictors of level of consciousness has been widely reported and models have included GCS score in multiple studies (Wind J. et.al, 2012), (Yee A.H. et. al., 2010) (Brieva J. et.al, 2014) (de Groot, et al., 2012) (Brieva J. et.al., 2013) (He X. et. al., 2015). Pupillary reflex is a lesser explored potential predictor among brain stem reflexes. It has been explored in the DCD-N (Yee A.H. et. al., 2010) and DCD-C (He X. et. al., 2015) prediction studies. The DCD-N study found pupillary reflex to be significantly association with outcome of death within 60 minutes in univariable analysis, but not in multivariable analysis and was not included in the final model. However, in the DCD-C model, the authors consider its inclusion in view of improved model performance (He X. et. al., 2015). We found pupillary reflex to be consistently assessed in all our study centers and it was considered to be among potential predictors that was an easily available measure in our cohort. In our new *ensemble* model, pupillary reflex was found to be an important predictor. Predictors of circulatory support and

haemodynamic variables have also been found to be important predictors in multiple studies (Wind J. et.al, 2012) (de Groot, et al., 2012) (Yee A.H. et. al., 2010) (Brieva J. et.al, 2014) (Brieva J. et.al., 2013) while systemic acidosis was explored in the study by Suntharalingam et. al. (Suntharalingam C., 2009). Predictors of age and admission diagnosis have been explored in some of the earlier studies (Wind J. et.al, 2012) (Yee A.H. et. al., 2010) (Cooke, Hotchkin, & Engelberg, 2010) with conflicting results. Inclusion of these potential predictors was meaningful in our evaluation for a generalised prediction model. Body mass index is a predictor that is intuitive though included only in the study by DaVila et. al.in their graft usability prediction model (Davila D. et.al, 2012). The graft usability model is also among studies to include ICU length of stay along with the recent DCD-C study that included hospitalization (He X. et. al., 2015).

6.2.b. Model performance

In 2017, Xu et. al, evaluated 4 existing tools in their prospective multicenter study sample of 219 Chinese neurocritical patients. These tools were assessed for their prediction of death within 120 minutes of WLST. They included the UNOS tool, the UWDCD-ET, and the two neurocritical-patient-specific tools of the DCD-N and DCD-C. The former two tools have been criticized over generalizability limiting their application in neurocritical patients. These models also have been repeatedly reported to be difficult to apply in view of the required inputs. Unlike our study, these models have been developed in retrospective study samples. Xu et. al. used a prospective multicenter study in 219 Chinese neurocritical patients for validating the tools. The reported AUC for predicting death within 120 minutes of WLST for the DCD-C model was 0.86 while that for DCD-N was 0.73. The reported AUC for UNOS was 0.51 and for UWDCD-ET

was 0.49. The AUCs for the optimism adjusted *classical* model in our study was 0.68 and for the *ensemble* model we developed, it was 0.64 in the test-set. The AUCs from the corresponding models including the physician's prediction predictor was 0.77 and 0.75. The DCD-C model was found to have the highest AUC value among the 4 models validated by Xu et. al. The DCD-C Nomogram was developed for prediction of death within 120 minutes of WLST in the Chinese neurocritical population and validated in the similar patient population. However, the authors of the study caution that the development study sample might have included some cases of brain-death along with DCD deaths (He X. et. al., 2015).

6.2.c. Inclusion of physician's prediction

Our findings are similar to the reports of a strong association of clinician's prediction of outcome to actual outcome in the studies by Brieva et.al. and Wind et.al. Wind et.al. found a specificity of 73% and sensitivity of 56% for prediction of death within 60 minutes of WLST in the Netherlands. In our study we do not assess for death within 60 minutes. For the prediction of death within 120 minutes of WLST, physician's prediction showed a specificity of 68.8%, and sensitivity of 76%.

Brieva et. al. developed a regression based and decision-tree model in two consecutive studies. Both models were developed for prediction of death within 60 minutes of WLST and include different patient pools from the same data for analysis in their two studies. They found ICU specialist opinion to be the best individual predictor of outcome in their studies. In their 2013 study using a regression approach with the inclusion of the ICU specialist opinion, they reported training-set AUC of 0.89 and test-set AUC of 0.84. Our new *classical* model had

training-set AUC of 0.84 and test-set AUC of 0.79. It is important to note that this 2013 study from Brieva et. al. was conducted in a sample of critically ill patients who underwent WLST who were not assessed separately for DCD eligibility after exclusion of instances of brain death. Furthermore, their main outcome was time to death within 60 minutes of WLST. It is difficult to compare the models as we cannot assess how their model would perform if applied to DCD eligible patients and a time to death within 120 minutes of WLST. In their 2014 study, however, they evaluate 318 'potential' DCD donors among critically ill patients undergoing WLST from their 2013 study population. The criteria adopted by authors to define 'potential' DCD donors differ from those of DCD eligibility guideline criteria. They use a decision tree approach, CART, to develop their models. Their model including ICU specialist opinion demonstrated an accuracy of 79%, sensitivity of 82% and PPV of 80% in the test-set for prediction of death within 60 minutes of WLST. The new *ensemble* model in our study that included physician's prediction, had an accuracy of 72%, sensitivity of 80% and PPV of 77% in the test-set for predicting death within 120 minutes. It is difficult to draw conclusion regarding model performance when assessing for prediction of death within different time bounds, even if we assume that the underlying samples are very similar. Existing models that were neither developed nor validated in DCD eligible patients could not be discussed in this section.

6.3. Strengths and weaknesses

There are multiple strengths in our study, both statistical and methodological that are worth noting. First, the prospective nature of the study was a major strength. A prospective study design prevents selection bias, since outcome is unknown at recruitment. If available, a

prospective study design enables collection of specific data elements of interest as necessary for the study with an opportunity to clarify collected data elements thus minimising measurement error. This is especially important in prediction model development which for the most part is performed using existing databases that were not necessarily developed for the model in question. This can often lead to important variables that are not in the database and therefore excluded from the model. Secondly, our study sample size of 307 adult DCD eligible patients is among the largest in existing literature, with the exception of the study by Brieva et. al. (Brieva J. et.al, 2014) with 318 'potential' DCD donors. The 'potential donor' assessment made by Brieva et al. was based only on age group and the lack of known malignancy criteria. Our study strictly applied the DCD eligibility criteria according to current guidelines which contain several considerations outside of age and malignancy. Though there are studies exploring prediction of time to death, very few studies focus on DCD eligible patients with eligibility as defined under standard and extended criteria in the DCD guidelines. DeVita et. al. analysed a subgroup of 'desirable DCD candidates' based on the UNOS criteria (DeVita M.A, 2008). Models developed using general ICU patients, who would not necessarily be eligible for DCD patients as they would not be generalizable. DCD eligible and DCD non-eligible patients may have very different co-morbidities and reasons for ICU admission leading to different time to deaths and potentially different effect estimates for given predictors. Finally, our study recruited patients from 15 centres across Canada and other centres internationally. As one of the main differences in time to death is possibly attributable to the way physicians perform the withdrawal of life-support, incorporating multiple centres with different practice patterns enhances the overall generalisability of our results. The statistical analysis that we carried out is also one of the main

strengths of this study. We developed two sets of models using different statistical approaches but all the while paying the utmost attention to avoid influencing predictor selection based on any statistical assessments of effect-size in our study population. Predictors included in a model play a vital role. Selection processes contingent on statistical measures of predictor effect-size in the developmental sample could lead to the identification of a model fitted to a specific segment of patient population. The performance of these models may not be transferred to a more generalised representation of the underlying patient population. DeVita et.al. used a variety of statistical approaches for predictor selection, starting with the CART approach. The final proposed model was inclusive of the node definition predictors from the 2 CART-based best models and additional variables entered in a step-wise regression from baseline status variables and withdrawal variables. While this model was developed in 505 critically ill patients undergoing WLST, it was then applied in the 95 identified 'desirable candidates' for DCD in the cohort. An important predictor in their model, off-mechanical-ventilation respiratory rate <8, was then dropped in the DCD subset due to small number of candidates. While Brieva et. al. also employed CART and logistic regression, their methodology was different from that of DeVita et.al. (Brieva J. et.al, 2014). To qualify for inclusion in the CART analysis, only those predictors that showed the strongest univariate associations with death within 60 minutes in their study sample comprising of critically ill patients undergoing WLST, were considered (Brieva J. et.al., 2013) (Brieva J. et.al, 2014). The authors decided to apply a CART approach in their DCD focussed analysis, and not logistic regression approach from their earlier study among critically ill patients undergoing WLST. This decision was based on a relatively small number of expected

outcome events in the development-dataset (80 outcome events) with relatively large number of potential predictors (16 predictors).

To summarise, we applied rigorous methodology to develop our prediction models. We used a purposive sampling in our multi-center, multi-national, prospective study design. We included DCD eligible patients from university-affiliated, mixed ICUs and dedicated our entire study sample of 307 patients (177 outcome events) to develop our models. We performed a careful, and though out *a priori* analysis plan. We developed two different models, using two statistical techniques, which contained evidence supported, clinically important potential predictors. We didn't apply predictor-selection restrictions based on their statistical effect-size in our study population and perform rigorous bootstrapped internal validation.

We recognise that our study has a number of limitations. Firstly, this was a non-intervention study which limited the collection of certain predictors. For example, although corneal reflex may be an important predictor in the literature it is not routinely performed in the ICU on all patients. As such we were not able to capture with an acceptable rate of missing data. Secondly, most of the predictors were collected around the time of WLST and very little information was available on the trajectory of the ICU patient. This may have limited the models' predictive ability. Thirdly, based on the bootstrap validation results, there may have been overfitting in our *classical* model. This may be a result of the study sample size or predictor number and would necessitate a future study with an even larger patient sample size. Fourthly, our aim was the prediction of death within 120 minutes of WLST drawing from clinically useful predictors. Given the non-interventional design, some predictors could have been missed which could have enhanced performance of the models. The *ensemble* model might have performed

better with the addition of these predictors. Considering a larger pool of potential predictors could have improvement the *classical* model performance, however, unlike in the case of the *ensemble* model only a restricted number could have been used. We observed that the *ensemble* model appeared to perform inferiorly compared to the *classical* model which might be attributable to a smaller than optimal dataset for this purpose. Lastly, although we performed a rigorous internal validation, our models were not externally validated.

6.4. Future studies

The accuracy of physician's prediction and enhancement of model performance upon its inclusion is an important finding and future research is needed to better understand and explain these results. Specifically, how are physicians arriving at their predictions and what predictors are being employed need further exploration. In addition, future studies will need to include additional predictors that would require interventions in order to collect the data. A future study would also require a larger sample size to best assess model performance. Within our current dataset we also plan to evaluate prior existing models and externally validate them in order to assess their performance in a temporally and geographically different population. We also plan to evaluate the association between the process of WLST and time to death. There is no single unifying practice when it comes to WLST amongst physicians and it is performed very differently in each center and also vary between centers. As such it will be vital to examine the effect of withdrawal practices on time to death. Finally, future studies are needed to assess the use of these models in clinical situations. We plan to further explore random forest classification approach to add new predictors from our assessments of the effect of withdrawal process and

study of physician's prediction-making process. We plan to use a stable model based on objective predictors to develop a software application, an *app*, to facilitate easy clinical use. Integrated knowledge translation efforts would be essential to bring in knowledge users and encourage adoption of this application into action. Knowledge dissemination and translation interventions would be needed to enhance understanding of the existing gaps and barriers in the areas of *app* usability and fine-tuning. Knowledge mobilization would encourage knowledge transfer through feedback from clinicians regarding perceived gaps in the *app* and identifying other existing gaps that could be addressed. Inclusion of the developed *app* in clinical use could lead to its further adaption and bolter wide spread use in the identification of potential DCD donors. A section of this *app* would be dedicated to patients' surrogate decision makers. This could potentially support the discussion-making process surrounding planning of level of care. This additional interactive section would be based on the feedback of the *app* users during knowledge translation interventions. This section would be accessible to non-clinician users on their mobile devises or computers. This section would be designed as an interactive knowledge sharing platform that presents the opportunity to understand the process, seek help to clarify any area, and understand possible scenarios applicable to their loved ones' individualised case. This might be particularly useful in the stressful scenario of impending permanent separation from a loved one. This could help them weigh-in with their priorities during the decision-making process. Decisions such as these, made under well-informed circumstances, could possibly relieve them from the burden of questioning if they would have decided differently if only they better understood all the aspects and how these applied to their context. This could help alleviate post-decision remorse during bereavement as found in organ donation studies (De Groot, et al.,

2015) and assist articulation when seeking support. Most importantly, this *app* with sections for the clinicians and for the surrogate decision makers, could keep the lines of communication transparent between the decision makers and provide an opportunity for all stakeholders to be in-synch. This might be considered as a highly efficient and effective approach assuming that the *app* is used as intended. However, integrated knowledge translation approach would be required in future stages to develop the envisioned *app,* for its continuous improvement and finally, its increasing inclusion in the DCD organ donation pathway.

CHAPTER 7: CONCLUSION

Our study is the first Canadian study to develop prediction models to determine death within 120 minutes of WLST in a cohort of DCD eligible patients. The study was carried out in mixed medical/ surgical ICUs of participating university-affiliated hospitals in three countries. We undertook a rigorous statistical approach to develop two models to predict death. Our methodology included a side by side analysis of models using a traditional (multivariable logistic regression) and a relatively new *ensemble* algorithm (random forest classification) approach. Our models may appear to perform less well than the models in the literature, but our model might be more generalizable and perform better in a larger sample of critically ill DCD eligible patients. For a true comparison, existing models and those developed in this study would have to be applied to a large external sample. We believe that exploring random forest classification could be beneficial in identifying an efficient prediction model based on objective predictors that could closely match the highly accurate, yet subjective predictions made by physicians. The robustness of the random forest approach would enable us to explore additional new clinically

important predictors while maintaining model stability in larger datasets. This would be very helpful in developing an online and mobile software applications for regular clinical use. Through improved awareness and feedback mechanisms from an integrated knowledge translation process, a readily applicable prediction tool could be developed to address the barriers and boost the adoption of DCD donation efficiently.

BIBLIOGRAPHY

(1968). *A definition of irreversible coma. Report of the Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death.* 337–340.: JAMA.

Amit Y., G. D. (1997). Shape quantization and recognition with randomized trees. *Neural Computation*, 1545–1588.

Austina, P., & Steyerberg, E. (2015). The number of subjects per variable required in linear regression analyses. *Journal of Clinical Epidemiology*, 627-636.

Bijoy V.T., L. C. (2013, October 27). *Novel application of Random Forest.* Retrieved from Clouds and the Earth's Radiant Energy System, NASA: https://ceres.larc.nasa.gov/documents/STM/2013-10/27_Bijoy_Random_Forest.pdf

Box, G., & Draper, N. (1987). *Empirical model-building and response surfaces.* New York: Wiley.

Breiman L. (2001). Bagging Predictors. *Machine Learning*, 123–140.

Breiman L. et. al. (1984). Classification and Regression Trees. *Chapman & Hall/CRC*.

Breiman, L. .., Cutler, A., Liaw, A., & Wiener, M. (2018, March 25). *Breiman and Cutler's Random Forests for Classification and Regression.* Retrieved from Cran.r-project.org: https://cran.r-project.org/web/packages/randomForest/randomForest.pdf

Brieva J. et.al. (2014). Prediction of Death in Less Than 60 Minutes After Withdrawal of Cardiorespiratory Support in Potential Organ Donors After Circulatory Death. *Transplantation*, 1112Y1118.

Brieva J. et.al. (2013). Prediction of Death in Less Than 60 Minutes Following Withdrawal of Cardiorespiratory Support in ICUs. *Critical Care Medicine*, 2677-2687.

(2016). *Canadian Institute of Health Information. e-Statistics Report on Transplant, Waiting List and Donor Statistics, 2014.* Ottawa, ON: CIHI.

Canadian Organ Replacement Register Inc., (. (2015). *CORR Annual Report: Treatment of End-Stage Organ Failure in Canada, 2004 to 2013.* Canadian Institute for Health Information (CIHI).

Chen R., D. Z. (2015). The Prediction of Malignant Middle Cerebral Artery Infarction: A Predicting Approach Using Random Forest. *Journal of Stroke and Cerebrovascular Diseases*, 958-964.

Coleman, N., Brieva, J., & Crowfoot, E. (2008). Prediction of death after withdrawal of life-sustaining treatments. *Crit Care Resusc*, 278–284.

Cooke, C., Hotchkin, D., & Engelberg, R. (2010). Predictors of Time to Death After Terminal Withdrawal of Mechanical Ventilation in the ICU. *Chest*, 289-297.

Couronné, R., Probst, P., & Boulesteix, A. (2018). Random forest versus logistic regression:a large-scale benchmark experiment. *BMC Bioinformatics* , 270 .

Cox, D. (1958). The regression analysis of binary sequences (with discussion). *J Roy Stat Soc B*, 215–242.

Davila D. et.al. (2012). Prediction Models of Donor Arrest and Graft Utilization in Liver Transplantation From Maastricht-3 Donors After Circulatory Death. *American Journal of Transplantation* , 3414–3424.

De Groot, J., van Hoek, M., Hoedemaekers, C., Hoitsma, A., Smeets, W., Vernooij-Dassen, M., & van Leeuwen, E. (2015). Decision making on organ donation: the dilemmas of relatives of potential brain dead donors. *BMC Med Ethics*, 16: 64.

de Groot, Y., Lingsma, H. F., Bakker, J., Gommers, D., Steyerberg, E., & Kompanje, E. (2012). External validation of a prognostic model predicting time of death after withdrawal of life support in neurocritical patients. *Crit Care Med*, 233–238.

DeLong, E., DeLong, D., & Clarke-Pearson, D. (1988). Comparing the Areas under Two or More Correlated Receiver Operating Characteristic Curves: A Nonparametric Approach. *Biometrics*, 837-845.

DeVita M.A, M. B. (2008). Donors After Cardiac Death: Validation of Identification Criteria (DVIC) Study for Predictors of Rapid Death. *American Journal of Transplantation*, 432-441.

Dhanani S. et.al. (2014). Vital signs after cardiac arrest following withdrawal of life-sustaining therapy: a multicenter prospective observational study. *Crit Care Med.* , 2358-2369.

Dietterich T. (2000). An Experimental Comparison of Three Methods for Constructing Ensembles of Decision Trees: Bagging, Boosting, and Randomization. *Machine Learning*, 139–157.

Dossetor JB. (1999). Death provides renewed life for some, but ethical hazards for transplant teams. *CMAJ : Canadian Medical Association Journal = Journal De L'Association Medicale Canadienne*, 160 (11): 1590-1.

Eighth plenary meeting-Committee A. (2004, May 22). *WHA57.18 Human organ and tissue transplantation,.* Retrieved from WHO: http://apps.who.int/gb/ebwha/pdf_files/WHA57/A57_R18-en.pdf

Evans, J., & Murphy, M. (2018, February 21). *Random Forests Model Selection and Performance Evaluation.* Retrieved from Cran.r-project.org: https://cran.r-project.org/web/packages/rfUtilities/rfUtilities.pdf

(2016). *Facing the facts.* The Kidney Foundation of Canada.

Finch, W., Finch, M., & Singh, M. (2016). Data imputation algorithms for mixed variable types in large scale educational assessment: a comparison of random forest, multivariate imputation using chained equations, and MICE with recursive partitioning. *Int. J. of Quantitative Research in Education*, 129 - 153.

Fugate J.E., S. M. (2011). Variability in donation after cardiac death protocols: A national survey. *Transplantation*, 386–389.

Gagnon YM, L. A. (2004). Treatment costs in Canada of health conditions resulting from chronic hepatitis B infection. *J Clin Gastroenterol* , S179–86.

Ghobrial, R., Freise, C., Trotter, J., Tong, L., Ojo, A., Fair, J., . . . Group, A. S. (2008). Donor Morbidity After Living Donation for Liver Transplantation. *Gastroenterology*, 468-476.

Greenland, S. (2008). Invited Commentary: Variable selection versus shrinkage in the control of multiple confounders. *Am J Epidemiol*, 623–629.

Guidelines and Protocols Advisory Committee. (2017, February 22). *Palliative Care for the Patient with Incurable Cancer or Advanced Disease Part 2: Pain and Symptom Management.* Retrieved from BCGuidelines.ca: https://www2.gov.bc.ca/assets/gov/health/practitioner-pro/bc-guidelines/palliative2.pdf

Harrell Jr, F. (2018, January 07). *Regression Modeling Strategies.* Retrieved from cran.r-project.org: https://cran.r-project.org/web/packages/rms/rms.pdf

He X. et. al. (2015). Nomogram for Predicting Time to Death After Withdrawal of Life-Sustaining Treatment in Patients With Devastating Neurological Injury. *American Journal of Transplantation*, 2136–2142.

He, Q., Morris, B., Grove, J., Petrovitch, H., Ross, W., Masaki, K., . . . Willcox, B. (2014). Shorter Men Live Longer: Association of Height with Longevity and FOXO3 Genotype in American Men of Japanese Ancestry. *Public Library of Science*.

Ho T.K. (1998). The Random Subspace Method for Constructing Decision Forests. *IEEE Transactions on Pattern Analysis and Machine Intelligence*, 832–844.

Huynh, T., M. Walling, A., Le, T., & Kleerup, E. (2013). Factors Associated with Palliative Withdrawal of Mechanical Ventilation and Time to Death after Withdrawal. *Journal of Palliative Medicine* , 1368-1374.

Knaus W.A., D. E. (1985). APACHE II: a severity of disease classification system. *Crit Care Med*, 818-29.

Koehrsen, W. (2017, Dec 27). *Random Forest Simple Explanation.* Retrieved from Medium: https://medium.com/@williamkoehrsen/random-forest-simple-explanation-377895a60d2d

Kuhn, M. (2018, May 27). *Classification and Regression Training.* Retrieved from Cran.r-project.org: https://cran.r-project.org/web/packages/caret/caret.pdf

Lewis. J et.al. (2003). Development of the University of Wisconsin Donation After Cardiac Death Evaluation Tool. *Progress in Transplantation*, 265-273.

Lo, C.-M., Fan, S.-T., Liu, C.-L., Chan, C.-S., & Wong, J. (2004). The Role and Limitation of Living Donor Liver. *Liver Transplantation*, 440 – 447.

Munshi L, D. S. (2015). Predicting time to death after withdrawal of life-sustaining therapy. *Intensive care medicine*, 41(6):1014-1028.

(2017). *Organ donation and transplantation in Canada- System progress report 2016 update.* Ottawa, ON: Canadian Blood Services.

(2016). *Organ donation and transplantation in Canada-System progress report 2006-2015.* Ottawa, On: Canadian Blood services.

Participants in the International Summit on Transplant Tourism and Organ Trafficking. (2008). The Declaration of Istanbul on Organ Trafficking and Transplant Tourism. *Nephrol Dial Transplant*, 3375–3380.

Peng S.Y., C. Y. (2010). Random forest can predict 30-day mortality of spontaneous intracerebral hemorrhage with remarkable discrimination. *Eur J Neurol*, 945-950.

Perlich, C., Provost, F., & Simonoff, J. (2003). Tree Induction vs. Logistic Regression: A Learning-Curve Analysis. *Journal of Machine Learning Research*, 211-255.

Prosperi M.C., M. S. (2014). Predicting phenotypes of asthma and eczema with machine learning. *BMC Med Genomics*, S7.

Rabeau Y. (2012). *The Economics of Kidney Failure.* The Kidney Foundation of Canada-Quebec Branch, www.kidney.ca/document.doc?id=3653.

Rabinstein A.A. et.al. (2012). Prediction of potential for organ donation after cardiac death in patients in neurocritical state: a prospective observational study. *The Lancet Neurology*, 414-419.

Reid A.W.N., H. S. (2011). Expansion of the kidney donor pool by using cardiac death donors with prolonged time to cardiorespiratory arrest. *Am J Transplant* , 995–1005.

Rhee J.Y., R. R. (2011). The impact of variation in donation after cardiac death policies among donor hospitals: A regional analysis. *Am J Transplant*, 1719–1726.

Robin, X., Turck, .., Hainard, A., Tiberti, N., Lisacek, F., Sanchez, J., . . . Siegert, S. (2018, May 06). *Display and Analyze ROC Curves.* Retrieved from Cran.r-project.org: https://cran.r-project.org/web/packages/pROC/pROC.pdf

Rogers W.A., d. L. (2011). Donation after cardiac death: Community views about 'decent' intervals. *Am J Transplant*, 583-590.

Shah, A., Bartlett, J., Carpenter, J., Nicholas, O., & Hemingway, H. (2014). Comparison of Random Forest and Parametric Imputation Models for ImputingMissing Data Using MICE: A CALIBER Study. *Am J Epidemiol.*, 764–774.

Shemie SD, B. A. (2006). National recommendations for donation after cardiocirculatory death in Canada: donation after cardiocirculatory death in Canada. *CMAJ* , 175:S1.

Shmueli, G. (2010). To Explain or to Predict? *Statistical Science*, 289-310.

Statistiques officielles 2017. (2018, March 13). Retrieved from Transplant Quebec: http://www.transplantquebec.ca/sites/default/files/statistiques_officielles_2017.pdf

Steyerberg, E. W. (2009). *Clinical prediction models: A practical approach to develpment, vallllidation, and updating.* Springer Science+Business Media, LLC.

Suntharalingam C., S. L. (2009). Time to cardiac death after withdrawal of life-sustaining treatment in potential organ donors. *Am J Transplant*, 2157–2165.

Taylor MC, G. P. (2002). Factors associated with the high cost of liver transplantation in adults. *Can J Surg*, 425–34.

Terner, M. e. (2016). Increasing Rates of Kidney Failure Care in Canada Strains Demand for Kidney Donors. *Healthcare Quarterly*, pp. 10-12.

The Madrid resolution on organ donation and transplantation: national responsibility in meeting the needs of patients, guided by the WHO principles. (2011). *Transplantation*, 29-31.

Transplantation, G. O. (2017). *Organ Donation and Transplantation Activities 2015.* Those [2015] data are based on the Global Observatory on Donation and Transplantation (GODT) data, produced by the WHO-ONT collaboration.

van Buuren, S., Groothuis-Oudshoorn, K., Robitzsch, A., Vink, G., Doove, L., Jolani, S., . . . Gray, B. (2018, July 27). *Multivariate Imputation by Chained Equations.* Retrieved from Cran.r-project.org: https://cran.r-project.org/web/packages/mice/mice.pdf

Vasiliadis HM, C. J. (2005). A cost-effectiveness and cost-utility study of lung transplantation. *J Heart Lung Transplant*, 1275–83.

Walter, S., & Tiemeier, H. (2009). Variable selection: current practice in epidemiological studies. *Eur J Epidemiol*, 733–736.

Wind J. et.al. (2012). Prediction of time of death after withdrawal of life-sustaining treatment in potential donors after cardiac death. *Crit Care Med*, 766-769.

Yee A.H. et. al. (2010). Factors influencing time to death after withdrawal of life support in neurocritical patients. *Neurology*, 1380-1385.

Zhu, X., & Wu, X. (2004). Class Noise vs. Attribute Noise: A Quantitative Study. *Artificial Intelligence Review*, 177–210.

Zielinski, A., Nazarewski, S., Bogetti, D., Sileri, P., Testa, G., & Sankary, H. B. (2003). Simultaneous pancreas kidney transplant from living related donor: A single center experience. *Transplantation*, 547–552.

APPENDICES

Appendix	Title	Page
1.a.	APPENDIX FIGURE 1: The United Network for Organ Sharing (UNOS) Criteria	102
1.b.	APPENDIX FIGURE 2: The University of Wisconsin DCD Evaluation Tool (UWDCD-ET)	103
2.a.	DePPaRT Protocol (supplementary document)	104
2.b.	DePPaRT Case report form (supplementary document)	104
3.	Expert opinion survey questionnaire	105
4.a.	APPENDIX FIGURE 3: Correlation matrix (Pearson)	107
4.b.	APPENDIX FIGURE 4: Correlation matrix (Spearman)	108
5	APPENDIX FIGURE 5: Receiver operating characteristic curve of the *classical* model with *a priori* potential predictors	109
6	APPENDIX TABLE 1: Post-hoc univariable logistic regression and description of the potential predictors by outcome	110
7	APPENDIX FIGURE 6: Plot of error rate vs number of trees for tuning the ensemble model with a priori selected predictors 114	112
8	APPENDIX FIGURE 7: Plot of error rate vs *mtry* at optimum number of trees selected for tuning of the *ensemble* model *with a priori* selected predictors	113
9	APPENDIX FIGURE 8: Receiver operating characteristic curve (ROC) and area under the curve (AUC) for *ensemble* random forest classification model with *a priori* predictors (Training-set)	114
10	APPENDIX FIGURE 9: Receiver operating characteristic curve (ROC) and area under the curve (AUC) for *ensemble*	115

random forest classification model with *a priori* predictors (Test-set)

11 APPENDIX FIGURE 10: Receiver operating characteristic curve (ROC) and area under the curve (AUC) for the *univariable* model with physician's prediction as predictor 116

12 APPENDIX FIGURE 11: Receiver operating characteristic curve (ROC) and area under the curve (AUC) for the new *classical* model with *a priori* selected and physician's prediction as potential predictors 117

13 APPENDIX FIGURE 12: Error plot vs number of trees for tuning new *ensembl*e model 118

14 APPENDIX FIGURE 13: Plot error rate vs *mtry* for tuning the new *ensemble* model 119

15 APPENDIX FIGURE 14: Receiver operating characteristic curve (ROC) and area under the curve (AUC) for new *ensemble* random forest classification model with *a priori* predictors and new predictor of physician's prediction (Training-set) 120

16 APPENDIX FIGURE 15: Receiver operating characteristic curve (ROC) and area under the curve (AUC) for new *ensemble* random forest classification model with *a priori* predictors and new predictor of physician's prediction (Test-set) 121

Supplementary Documents 122

A2. a. DePPaRT Protocol (supplementary document)

A2. b. DePPaRT Case report form (supplementary document)

APPENDIX 1a

APPENDIX FIGURE 1:The United Network for Organ Sharing (UNOS) Criteria

Characteristics at time of withdrawal of life-sustaining treatments
UNOS criteria
Apnea
RR < 8 (i.e. RR 1–7)
RR > 30
LVAD
RVAD
V-A ECMO
Pacemaker-unassisted heart rate <30
PEEP≥ 10 and SaO_2≤ 92%
FiO_2≥ 0.5 and SaO_2≤ 92%
V-V ECMO
Norepinepherine or phenylephrine ≥0.2
Dopamine≥15
IABP1:1 or (dobutamine or dopamine ≥10 and CI ≤ 2.2)
IABP1:1 and CI ≤ 1.5
Number of UNOS criteria present
0
1
2
3
4–5

Donors with no criteria might be excluded
At least one criteria for DCD conideration with 50% failure rate
Ref: Validation study by DeVita et. al. (2008)

APPENDIX 1b

APPENDIX FIGURE 2: The University of Wisconsin DCD Evaluation Tool (UWDCD-ET)

Criteria	Assigned Points	Pt. Score
Spontaneous Respirations after 10 min.		
Rate >12	1	
Rate <12	3	
TV >200 cc	1	
TV <200 cc	3	
NIF <20	3	
NIF >20	1	
No Spontaneous Respirations	9	
Vasopressors/Inotropes		
No Vasopressors/Inotropes	1	
Single Vasopressor/Inotropes	2	
Multiple Vasopressors/Inotropes	3	
Patient Age		
0-30	1	
31-50	2	
51 +	3	
Intubation		
Endotracheal tube	3	
Tracheostomy	1	
Oxygenation After 10 minutes		
O2 Sat >90%	1	
O2 Sat 80-89%	2	
O2 Sat <79%	3	
	Final Score	
	Time from Extubation to Expiration	

Ref: Lewis et.al.(2003)

APPENDIX 2a: DePPaRT Protocol (Supplementary document)

APPENDIX 2b: DePPaRT Case report form (Supplementary document)

APPENDIX 3: Expert opinion survey questionnaire

Expert Opinion Questionnaire

1 **Page 1** 2 Page 2 3 Page 3 4 Page 4

Predicting time to death after withdrawal of life-sustaining therapy in potential organ donors: A secondary analysis of a multicenter prospective observational study.

Our aim:

To develop a new prediction tool to assess time to death, utilizing precise set of patient information available preceding withdrawal of life sustaining therapy (WLST) in order to enhance the identification of patients eligible for donation after cardio-circulatory death (DCD).

Our research plan:

To perform a secondary analysis of the Death Prediction and Physiology after Removal of Therapy (DePPaRT) study.

Approaches to identify important potential predictors of time to death at WLST:

- Systematic review of the literature for risk factors/ risk prediction models
- Expert opinion on the important potential predictors
- Exploratory analysis of data from DePPaRT study

Purpose of this questionnaire:

To seek expert opinion on important potential predictors of time to death at WLST to inform the third approach.

Listed below are available candidate variables from the DePPaRT study database. Kindly rate these variables, on a scale of 1(low) – 4 (high), according to their importance as potential predictors of time to death at the time of WLST.

This study is supported by the FRQS training award funds. Participation in this survey is voluntary. All answers provided by the survey respondents will be treated as confidential and aggregated with other responses in the reporting. No survey comments or other responses will be attributed to an individual. We thank you for sharing your expert opinion and supporting this study.

Email *

Date Completed *

Next

1 / 4

① Page 1 ② **Page 2** ③ Page 3 ④ Page 4

DEMOGRAPHIC & BASELINE INFORMATION: *

1 [Low]- 4 [High]

	1	2	3	4
Age *	○	○	○	○
Gender *	○	○	○	○
BMI *	○	○	○	○
Admission Diagnosis *	○	○	○	○
Cardiac arrest with resuscitation measures within the past 24 hours *	○	○	○	○
APACHE II Score *	○	○	○	○
Comorbidities *	○	○	○	○

Back Next

① Page 1 ② Page 2 ③ **Page 3** ④ Page 4

INFORMATION AT WLST (Respiratory & Circulatory) *

1 [Low] - 4 [High]

	1	2	3	4
Mode of Ventilation *	○	○	○	○
Airway Type (e.g. endotracheal tube, tracheotomy, nasal cannula, face mask, etc.) *	○	○	○	○
Respiratory Rate *	○	○	○	○
Positive End Expiratory Pressure *	○	○	○	○
PaO_2 or FiO_2 Threshold *	○	○	○	○
Oxygenation Index *	○	○	○	○
Systolic BP *	○	○	○	○
Vasopressors and Inotropes *	○	○	○	○
Circulatory Therapy (e.g. ECMO, CRRT, LVAD etc.) *	○	○	○	○

Back Next

① Page 1 ② Page 2 ③ Page 3 ④ **Page 4**

INFORMATION AT WLST (Metabolic, Neurological & Other) *

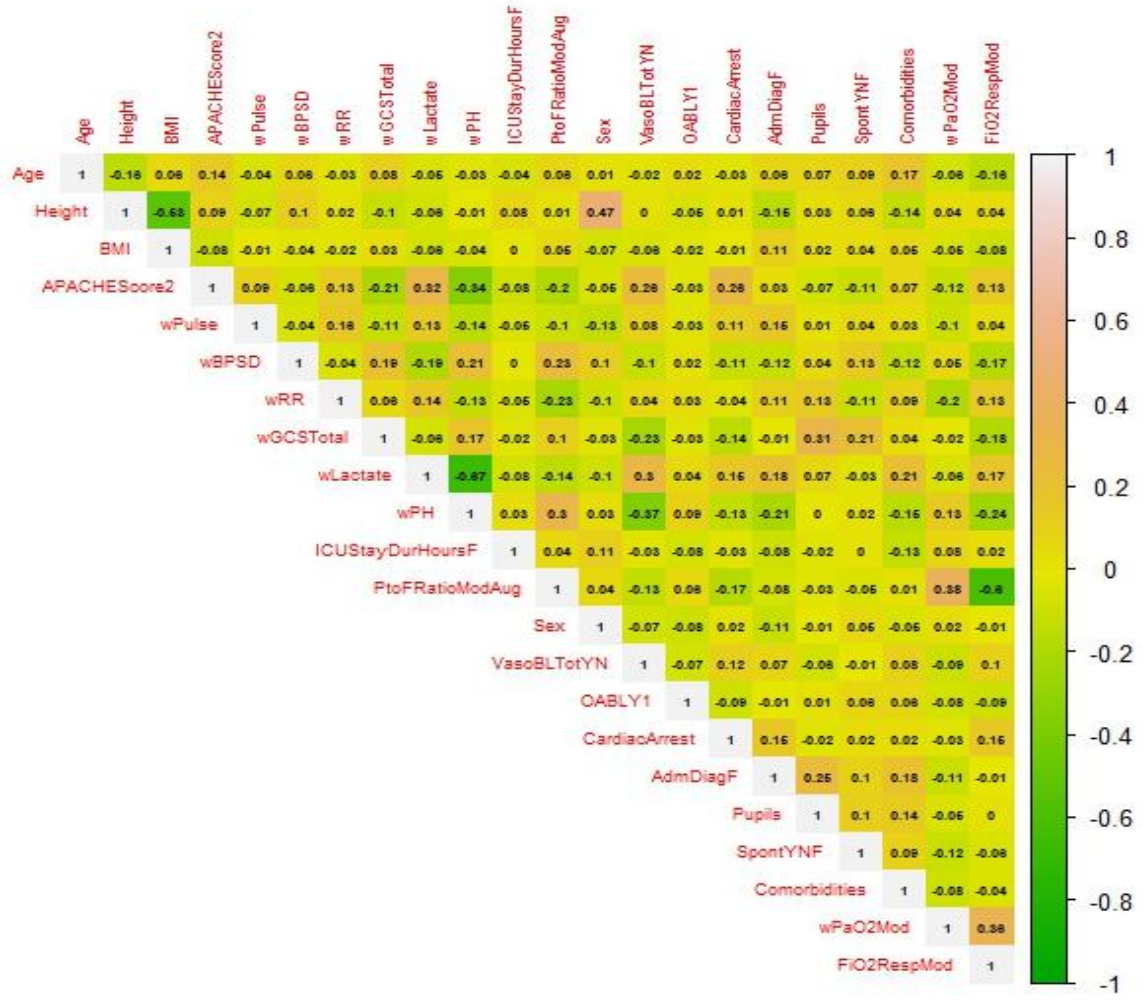
1 [Low] - 4 [High]

	1	2	3	4
GCS *	○	○	○	○
Absent Cough/ Gag Reflex *	○	○	○	○
Absent Corneal Reflex *	○	○	○	○
Absent/ Extensor Motor Reflex *	○	○	○	○
Analgesia Level *	○	○	○	○
CT Head Findings *	○	○	○	○
pH *	○	○	○	○
Lactate Levels *	○	○	○	○
ICU Length of Stay *	○	○	○	○

Back Submit

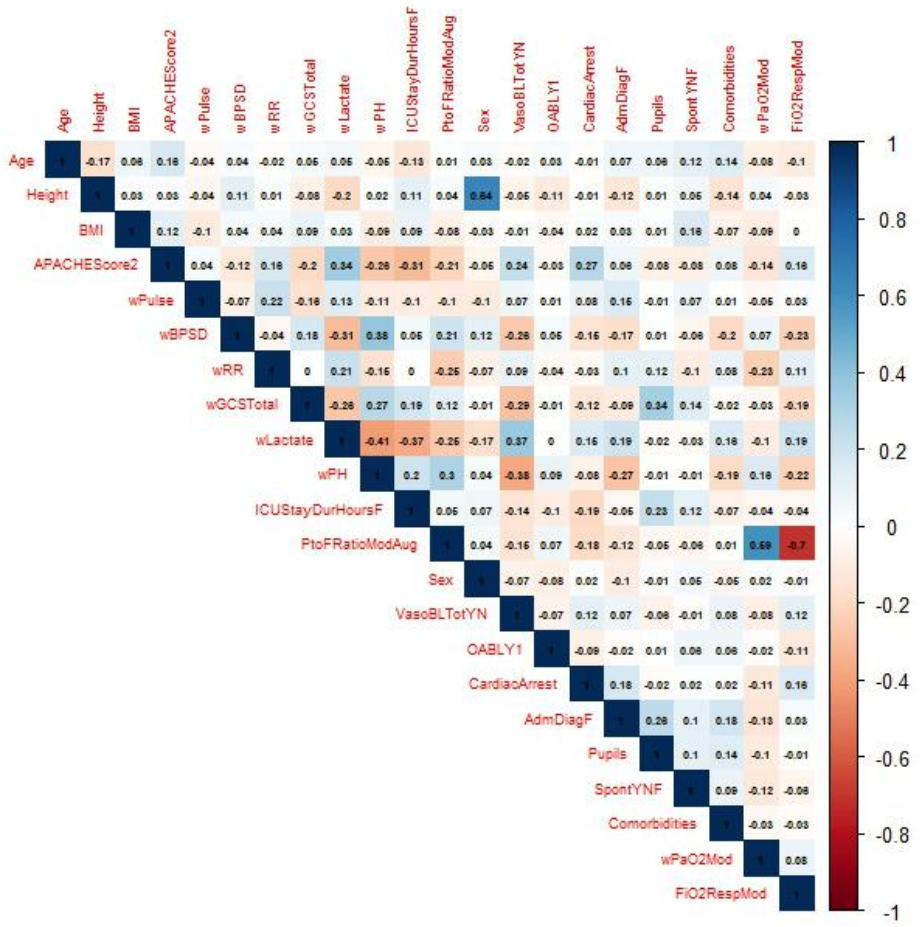
APPENDIX 4a

APPENDIX FIGURE 3: Correlation matrix (Pearson)



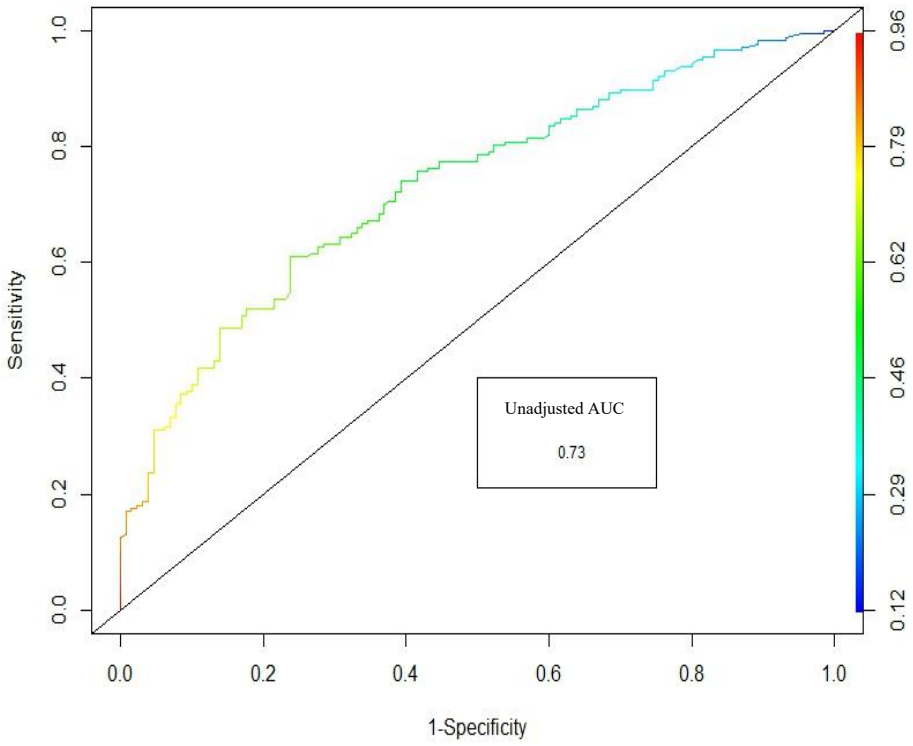
APPENDIX 4b

APPENDIX FIGURE 4: Correlation matrix (Spearman)



APPENDIX 5

APPENDIX FIGURE 5: Receiver operating characteristic curve of the *classical* model with *a priori* potential predictors



Adjusted AUC
0.66

Appendix 6

APPENDIX TABLE 1: Post-hoc univariable logistic regression and description of the potential predictors by outcome

Potential predictors	Time to death ≤120 minutes ʃ	Time to death >120 minutes ʃ	Odds Ratio (95%CI)	P (Wald's test)
Age (Years)	Missing 0 56.36 ± 14.8	Missing 0 61.34 ± 12.4	0.97 (0.96,0.99)	0.002 *
Sex [Male vs Female]	Missing 0	Missing 0	0.73 (0.46,1.17)	0.188
Male	58.8%	66.2%		
Female	41.2%	33.8%		
Height (cm)	Missing 16 172 ± 12.9	Missing 17 172 ± 13.8	1.00 (0.98,1.02)	0.738
Admission Diagnosis	Missing 0	Missing 0		
Traumatic brain injury [reference]	18.6%	15.4%		
Non-traumatic brain injury neurological	32.2%	39.2%	0.68 (0.35,1.33)	0.256
Medical	44.1%	40.8%	0.89 (0.46,1.72)	0.733
Surgery (non-traumatic brain injury)	5.1%	4.6%	0.91 (0.28,2.94)	0.873
Comorbidities	Missing 15	Missing 8		
None [reference]	31.5%	25.4%		
Other	35.8%	30.3%	0.89 (0.50,1.60)	0.709
Cardio-respiratory	32.7%	44.3 %	0.64 (0.37,1.12)	0.117
BMI (kg/m2)	Missing 16 30.35 ± 12.3	Missing 17 29.79 ± 21.6)		
≥30	34.2%	27.4%	1.31 (0.80,2.14)	0.291
<30 [reference]	65.8%	72.6%		
APACHE II Score	Missing 0 26.98 ± 7.9	Missing 0 25.32 ± 7.6		
< 15 [reference]	5.1%	5.4%		
15-24	31.6%	44.6%	0.75 (0.26,2.15)	0.594
≥ 25	63.3%	50%	1.34 (0.48, 3.77)	0.579
ICU stay duration (in hours)	Missing 0 236.33 ± 900.4	Missing 0 28.59 ± 921.0	0.9999 (0.9997,1.0002)	0.675
At one-hour pre-WLST				
Cardiac arrest with resuscitation in 24 hours pre-WLST	Missing 0	Missing 0		
Yes	Yes 14.7%	16.2%	0.89 (0.48,1.67)	0.725
No [reference]	No 85.3%	No 83.8%		
Vasopressor use 1-hour pre-WLST	Missing 0	Missing 0		
Yes	44.6%	28.5%	2.03 (1.25,3.28)	**0.004** *
No [reference]	55.4%	71.5 %		
Systolic blood pressure (mm Hg) [≤ 100 vs >100]	Missing 2 118.77 ± 37.0	Missing 2 137.98 ± 78.5		
≤ 100	0 33.1%	0 17.2%	2.33 (1.34,4.02)	**0.003** *
>100 [reference]	1 66.9%	1 82.8%		
Pulse raAPPEte (rate per minute)	Missing 1 92.05 ± 24.5	Missing 1 91.40 ± 22.2	1.00 (0.99,1.01)	0.727

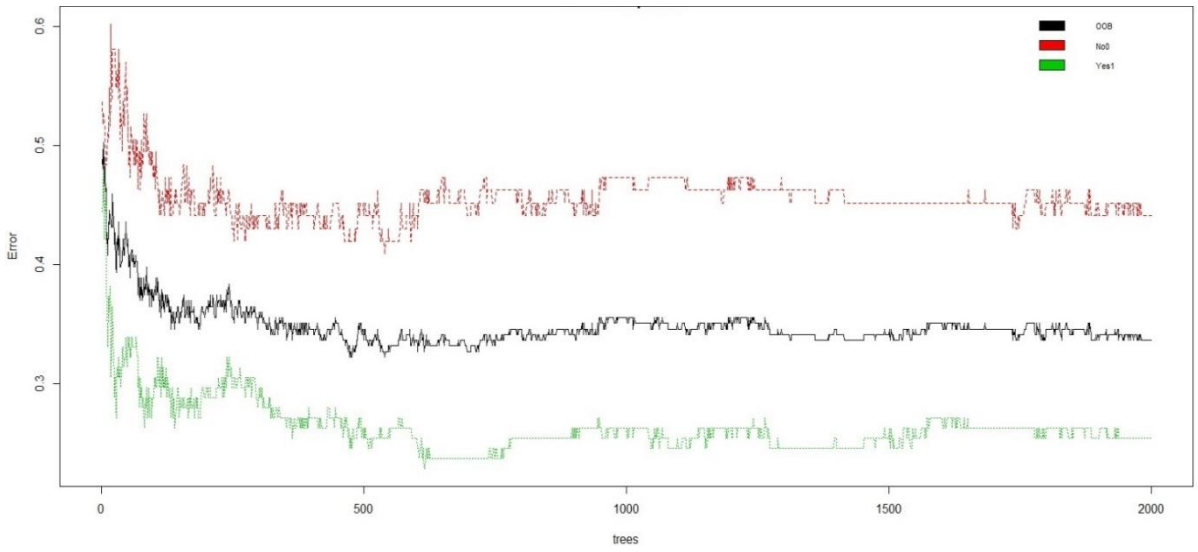
Potential predictors	Time to death ≤120 minutes ʃ	Time to death >120 minutes ʃ	Odds Ratio (95%CI)	P (Wald's test)
Lactate (mmol/L)	Missing 12 4.17 ± 6.5	Missing 7 1.90 ± 2.9	1.14 (1.05,1.23)	**0.002** *
pH	Missing 8 7.36 ± 0.2	Missing 8 7.43 ± 0.1	0.01 (0.00,0.07)	**< 0.001** *
Opioid analgesic use 1-hour pre-WLST	Missing 0	Missing 0		
Yes	19.8%	17.7%	1.15 (0.64,2.05)	0.645
No [reference]	80.2%	82.3%		
GCS score	Missing 3 3.84 ± 1.6	Missing 3 4.98 ± 2.5		
GCS score 3	67.8%	42.5%	2.80 (1.75,4.47)	**< 0.001** *
GCS score >3 [reference]	32.2%	57.5%		
Pupillary reflex	Missing 6	Missing 4		
Yes	63.2%	78.6%	0.52 (0.31,0.87)	**0.013** *
No [reference]	36.8%	21.4%		
PaO2	Missing 8 114 ± 58.3	Missing 8 110 ± 48.7	1.00 (0.997,1.01)	0.665
FiO2	Missing 8 55.3 ± 26.3	Missing 8 42.1 ± 21.9	1.02 (1.01,1.03)	**<0.001***
PaO2/ FiO2 ratio	Missing 11 234.40 ± 11.5	Missing 11 281.99 ± 107.0		
≤100 [reference]	12.7%	4.2%		
101-200	30.1%	19.3%	0.61 (0.22,1.70)	0.342
>200	57.2%	76.5%	0.3 (0.12, 0.77)	**0.013***
Respiratory rate (Breaths/ minute)	Missing 1 19.94 ± 8.7	Missing 1 19.26 ± 7.1		
<12 [reference]	10.8%	10.1%		
12-25	64.2%	74.4%	0.80 (0.38,1.71)	0.572
>25	25%	15.5%	1.51 (0.62,3.63)	0.363
Spontaneous respiration	Missing 35	Missing 37		
Yes	8.5 %	12.9%	0.66 (0.30,1.45)	0.298
No [reference]	91.5%	87.1%		
Physician's prediction [Yes vs No] Å	50.5%	36.8%	6.98 (4.18,11.67)	**< 0.001***

ʃ Values are presented as Mean ± SD
ʃ Counts are presented as % of complete available data
ʃ Counts are presented for missing (not included to calculate proportion s mentioned above)
BMI = body mass index;
CI = confidence interval
FiO2 = fraction of inspired oxygen;
GCS = Glasgow coma scale
ICU = intensive care unit
OR = odds ratio
PaO2 = partial pressure arterial oxygen;
WLST = withdrawal of life-sustaining therapy

Å= missing 39(12.7%)

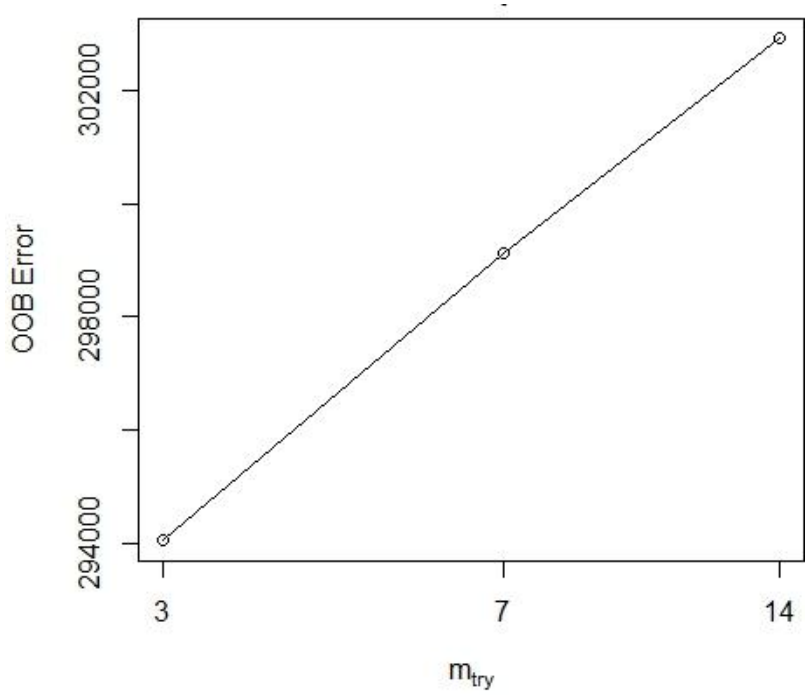
APPENDIX 7

APPENDIX FIGURE 6: Plot of error rate vs number of trees for tuning the *ensemble* model with *a priori* selected predictors



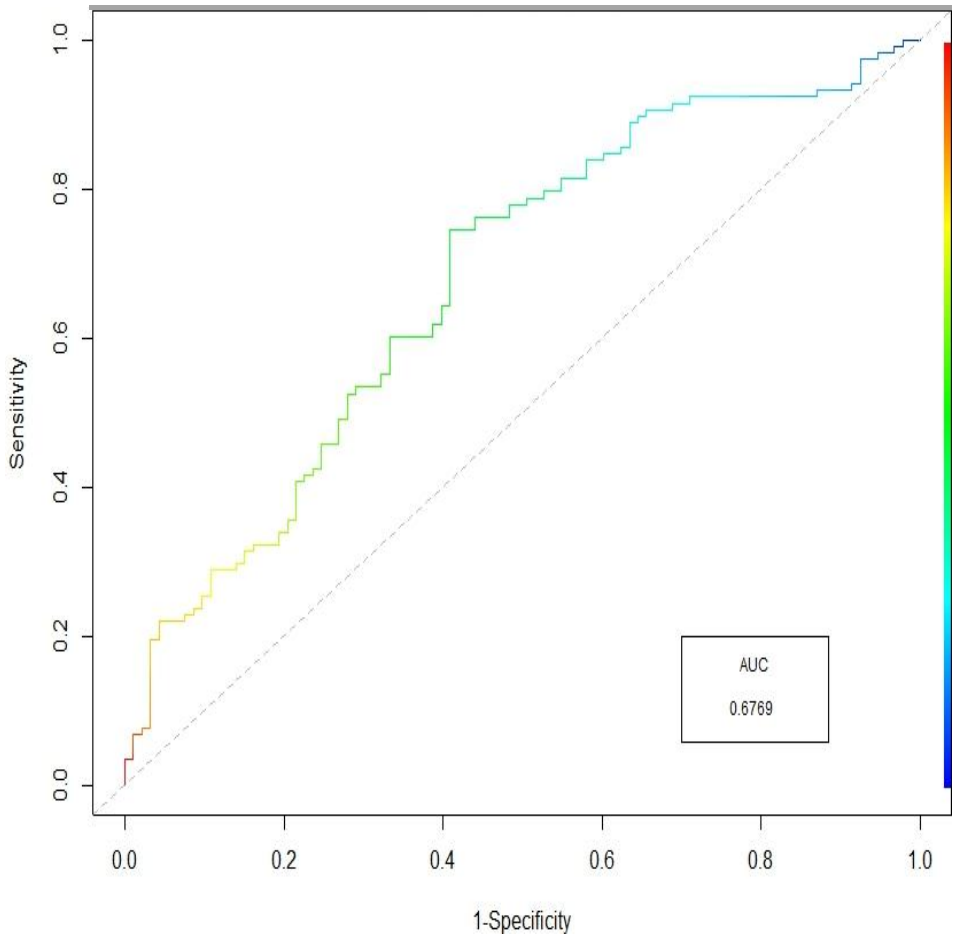
APPENDIX 8

APPENDIX FIGURE 7: Plot of error rate vs *mtry* at optimum number of trees selected for tuning of the *ensemble* model with *a priori* selected predictors



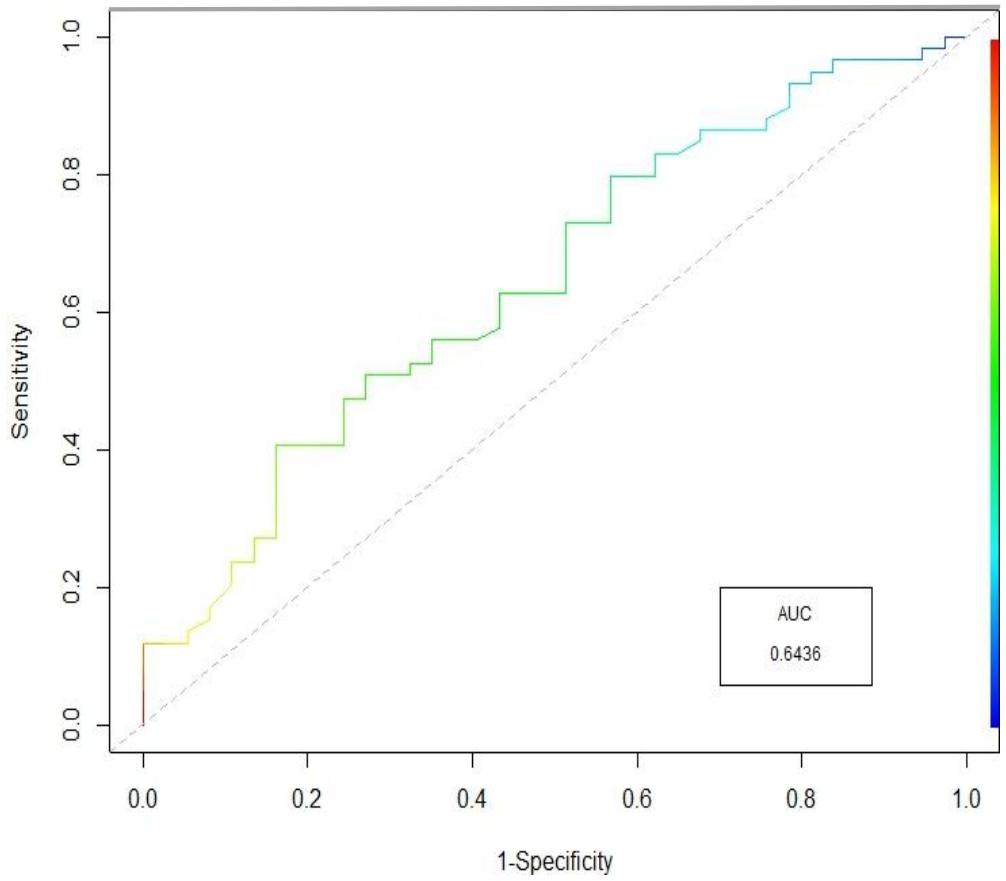
APPENDIX 9

APPENDIX FIGURE 8: Receiver operating characteristic curve (ROC) and area under the curve (AUC) for *ensemble* random forest classification model with *a priori* predictors (Training-set)



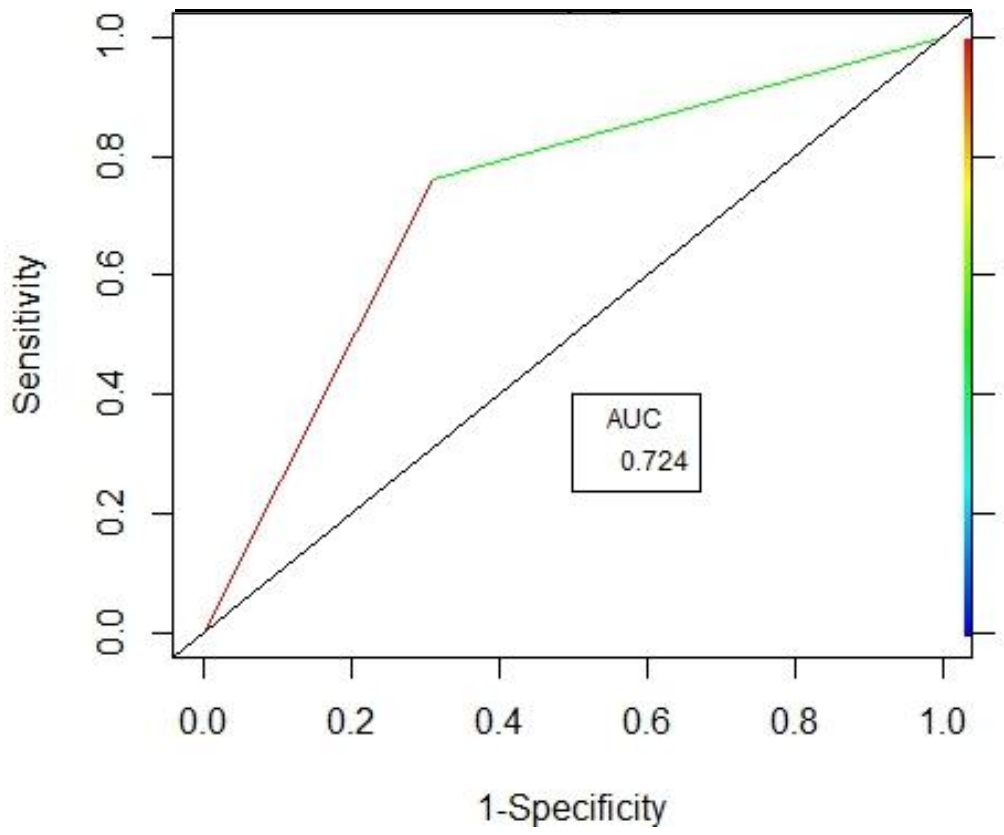
APPENDIX 10

APPENDIX FIGURE 9: Receiver operating characteristic curve (ROC) and area under the curve (AUC) for *ensemble* random forest classification model with *a priori* predictors (Test-set)



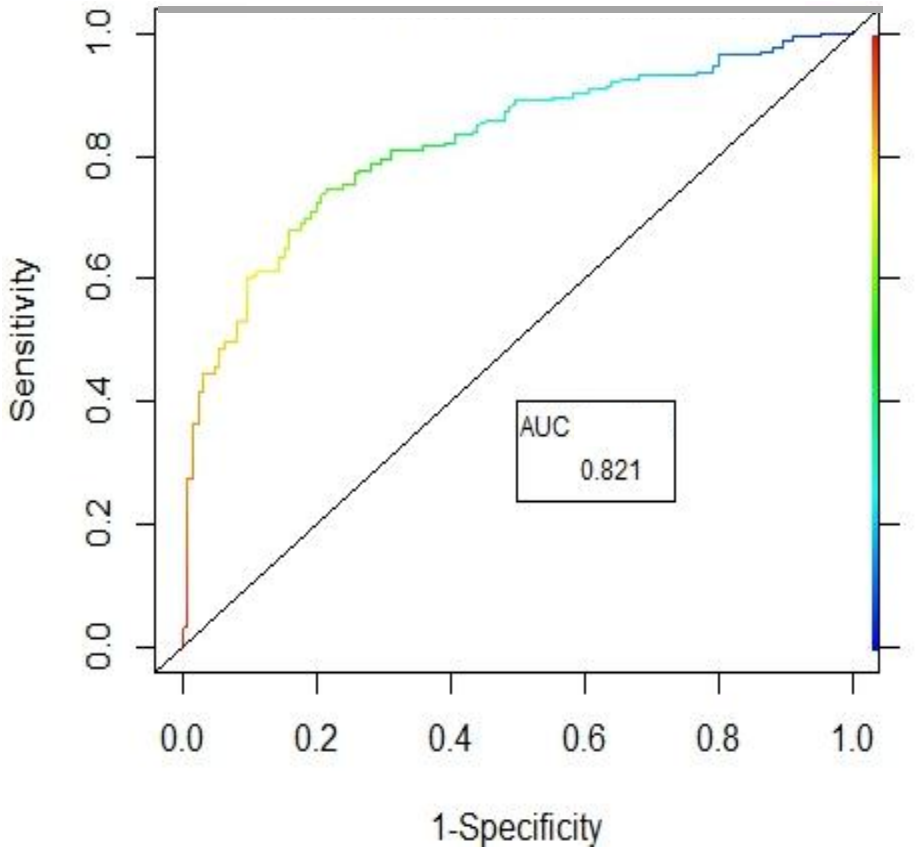
APPENDIX 11

APPENDIX FIGURE 10: Receiver operating characteristic curve (ROC) and area under the curve (AUC) for *univariable* model with physician's prediction as predictor



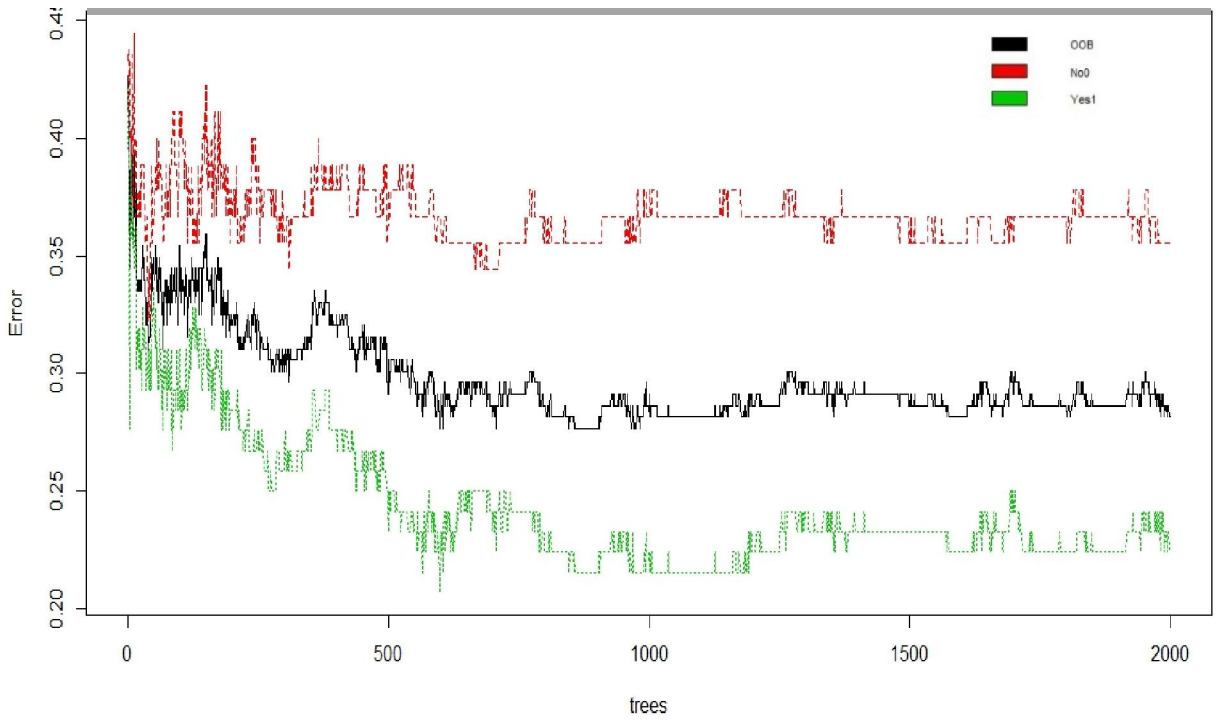
APPENDIX 12

APPENDIX FIGURE 11: Receiver operating characteristic curve (ROC) and area under the curve (AUC) for the new *classical* model with *a priori* selected and physician's prediction as potential predictors



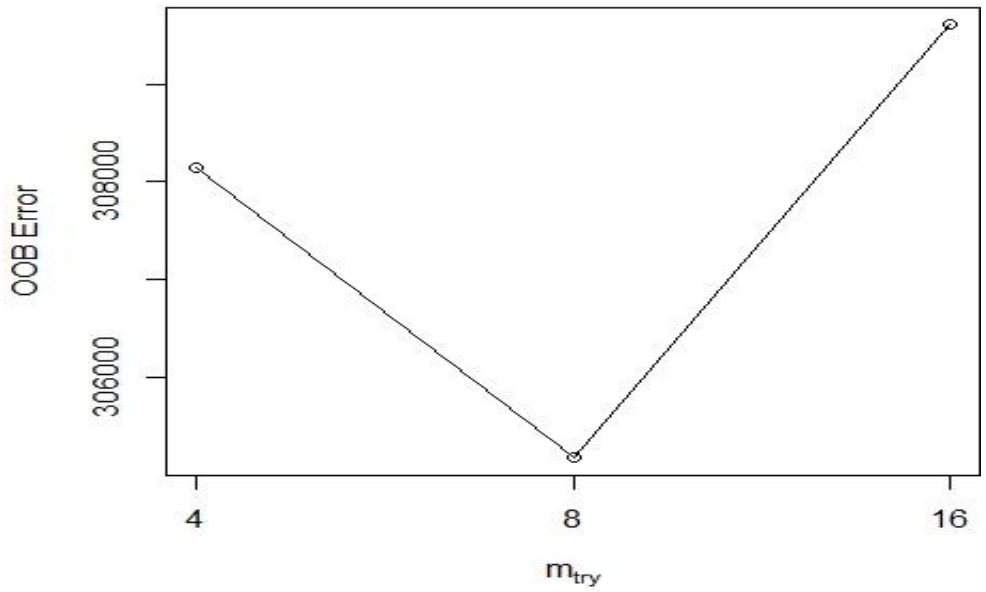
APPENDIX 13

APPENDIX FIGURE 12: Error plot vs number of trees for tuning new *ensemble* model



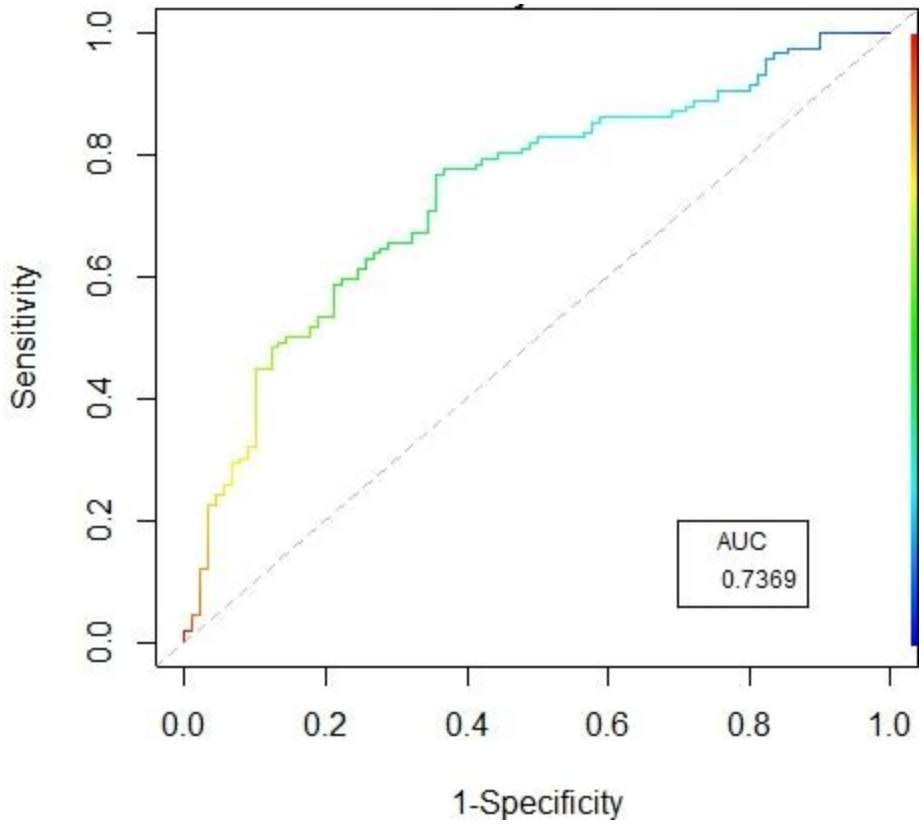
APPENDIX 14

APPENDIX FIGURE 13: Plot error rate vs *mtry* for tuning the new *ensemble* model



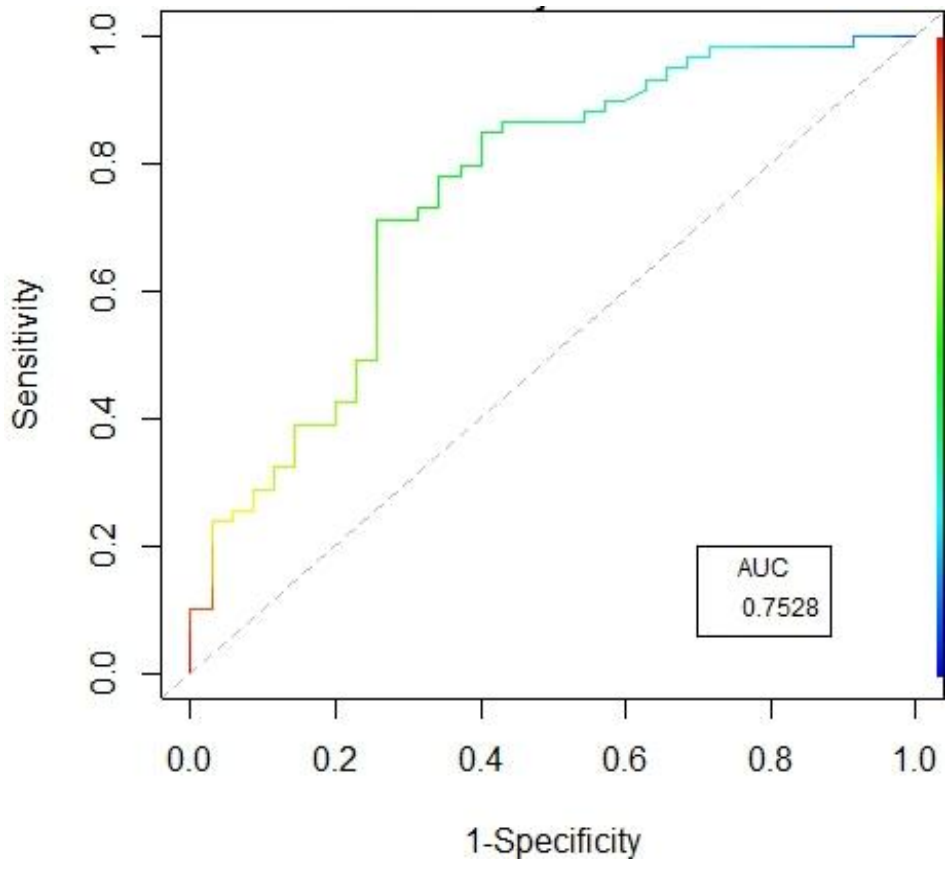
APPENDIX 15

APPENDIX FIGURE 14:Figure 12: Receiver operating characteristic curve (ROC) and area under the curve (AUC) for new *ensemble* random forest classification model *with a priori* predictors and new predictor of physician's prediction (Training-set)



APPENDIX 16

APPENDIX FIGURE 15: Receiver operating characteristic curve (ROC) and area under the curve (AUC) for new *ensemble* random forest classification model with *a priori* predictors and new predictor of physician's prediction (Test-set)



Supplementary Documents

A2. a: DePPaRT Protocol (APPENDIX 2a)

Death Prediction and Physiology after Removal of Therapy (DePPaRT)

Prediction of Time to Death and Description of Physiologic Function During the Dying Process following Withdrawal of Life-Sustaining Therapy: An Observational Study

Study Protocol

Principal Investigator: **Sonny Dhanani, MD, FRCPC** [1]
Co-Investigators & Collaborators: **See Appendix A**
Project Manager: **Laura Hornby, MSc** [2]
Central Research Coordinator: **Amanda van Beinum, MSc**
Administrator: **Paulina Mirsky**[2]

1. Pediatric Critical Care, Children's Hospital of Eastern Ontario (CHEO); Chief Medical Officer (organ donation), Trillium Gift of Life Network; Organ Donation Physician Champion, CHEO; Member, The Bertram Loeb Consortium in Organ and Tissue Donation, Faculty of Arts, University of Ottawa; Assistant Professor, Faculty of Medicine, University of Ottawa
2. See Appendix A

TABLE OF CONTENTS

1. LAY ABSTRACT 4
2. INTRODUCTION....4
3. RESEARCH QUESTIONS, HYPOTHESES & OBJECTIVES 7
3.1 Principal Study: Physiologic Function During the Dying Process, Following Withdrawal of Life Sustaining Therapy 7
3.2 Complementary Study 1: Prediction of Time to Death Following Withdrawal of Life Sustaining Therapy 7
4. BACKGROUND/PRESENT STATE OF KNOWLEDGE/RATIONALE 8
4.1 General State of Deceased Organ Donation in Canada 8
4.2 Re-emergence of Donation after Circulatory Determination of Death (DCD) 8
4.3 Cessation of Cardiac Activity and Function During the Dying Process....9
4.4 Cessation of Neurologic Activity and Function During the Dying Process....10
4.5 Prediction Tool for Time to Death after Cardiac Arrest 10
4.6 DDePICt Pilot Study....12
4.7 Rationale For Multicentre Observational Study 12
5. RESEARCH DESIGN/METHODS/ANALYSIS 13
5.1 Study Design 13
5.1.1 Study Population 13
5.2 Methods....15
5.2.1 Subject Recruitment 15
5.2.2 Study Procedures 16
5.3 Outcome Measures....17
5.3.1 Principal Study (Physiologic Function During the Dying Process Following WLST)....17
5.3.2 Complementary Study 1 (Prediction of Time to Death Following WLST 17
5.4 Data Collection and Management 18
5.4.1 General Information Variables 18
5.4.2 Variables Specific to the Principal Study (Physiologic Function During the Dying Process Following WLST) only....18
5.4.3 Variables Specific to Complementary Study 1 (Prediction of Time to Death Following WLST) only 19
5.5 Statistical Analysis 20
5.5.1 Sample Size 20
5.5.2 Analysis 21
6. STUDY MANAGEMENT....22
6.1 Personnel....22

6.2 Patient Screening and Enrolment....23
7. RISKS/ETHICAL CONSIDERATIONS....23
8. DISSEMINATION OF RESULTS....24
9. STUDY MILESTONES....24
10. IMPACT....25
11. RELEVANCE TO CHILD HEALTH....25
12. FUTURE DIRECTIONS....26
13. BUDGET AND JUSTIFICATION....27
14. APPENDICES....28
14.1 Appendix A – Study Members....28
14.2 Appendix B – Pilot Study Manuscript....32
14.3 Appendix C – Systematic Review of Time to Death Predictors....34
14.4 Appendix D – Eligibility Criteria for DCD....37
14.5 Appendix E – Consent Forms and Letters of Invitation to Participate....38
14.6 Appendix F – Study Period of Data Collection....39
14.7 Appendix G – Information System Requirements....40
14.8 Appendix H – Data Collection Tools....42
14.9 Appendix I – Letters of Support....49
14.10 Appendix J – Budget Justification....51
14.11 Appendix K – Complementary Study 2....55
15. REFERENCES....76

1. LAY ABSTRACT

The demand for transplantable organs continues to out-pace the supply. Current accepted practice is to donate organs after the neurologic determination of death (also known as "brain death"). Due to improved technologies for preserving organs as well as severe shortages of organs for transplantation, reconsideration of another type of organ donation: donation after circulatory determination of death has emerged. For this type of donation, a critically ill patient who is not expected to survive is disconnected from the ventilator (breathing-machine), their breathing and heart stops and a short time later they are pronounced dead and their organs are removed for transplantation. Medical standards for the determination of brain death have been established and they are generally well accepted in most countries. However, similar standards for circulatory determination of death vary within and between countries. Patient safety and public trust in organ donation rely on clear and acceptable guidelines to ensure a safe diagnosis of death.

The proposed multicentre study is part of the larger DDePICt (Death Determination Practices in Intensive Care Units) research program. It will build on information gathered from: a feasibility study of the determinants of death after cardiac arrest; a related survey of all critical care physicians in Canada; and a review of the literature. The study will record the biological changes of the heart and brain during the dying process, following withdrawal of life-sustaining therapy. It will also collect information that will be used to help physicians better predict how long it will take someone to die after withdrawal of life-sustaing therapy. In addition, the experience of families regarding their decisions about consenting to organ donation and participating in end of life research, will be described.

This is the first large, international study whose purpose is to systematically record the activity and function of the heart and brain during the dying process in both adults and children. This large, controlled, study will provide information to respond to continued calls for more research in this area by acquiring much needed scientific data to address concerns about how to determine death using circulatory criteria. This information will help establish accepted medical practices in this area and ensure an increase in organ donation. In Canada, The Loeb Chair and Research Consortium in Organ and Tissue Donation and the Canadian Critical Care Trials Group support this project. In the United Kingdom, the UK National Organ Donation Committee and UK NHS Blood and Transplant also fully support the study. The Canadian Institute of Health Research (CIHR) is funding the Canadian arm of this project as part of the Canadian National Transplant Research Program. Further funding for the international expansion is pending.

2. INTRODUCTION

The shortage of transplantable organs is a global problem. Moreover, The World Health Organization (WHO) has challenged nations to begin to address this serious medical health issue by, among other objectives, improving their national systems for both living and deceased donation[1]. All countries will find this challenge difficult to meet. In Canada, there has been little increase in deceased donors over the past five years[2] and

now 4,415 Canadians are on active transplant waiting lists[3]. The growing imbalance between supply and demand for organs means that Canadians needing a transplant face a 30–40% lifetime probability of never receiving one.[4] In the United Kingdom, despite increasing donation by 50% over five years, it is estimated that three people die per day awaiting a life-saving transplant[5].

Organ donation after neurologic determination of death (NDD, also known as brain death) continues to be the dominant source of organs for transplantation. Recently, the practice of donation after circulatory determination of death (DCD) has become an important source for organs. This has allowed some countries, notably the United Kingdom and the Netherlands to expand their donor pool. In these two countries DCD accounts for over 40% of all their deceased donations[6]. However, this practice has not been broadly implemented in Canada primarily because of logistic and ethical concerns. For DCD to expand in a broader international environment, further information regarding the timing and patterns of cessation of cardiac and neurologic function after cardiac arrest is required.

This study, entitled "Death Prediction and Physiology after Removal of Therapy" (DePPaRT), is expected to have an immediate impact on patients waiting for transplantation in Canada and the international community. The DePPaRT study represents the fourth phase of the Canadian led Determination of Death Practices in Intensive Care (DDePICt) program, aimed at defining the determinants of death after cardiac arrest in critically ill adults and children for the purposes of organ donation. Based on results from our pilot study[7] (see Appendix B), we are proposing to carry out a study that will gather much needed information about the physiology of the dying process.

The primary objective of the study will be to determine the incidence of autoresuscitation in critically ill patients who die in the intensive care unit (ICU), following withdrawal of life-sustaining therapy (WLST). We define autoresuscitation as an unassisted return of spontaneous circulation after a determination of death. Secondary objectives include: documenting the pattern of cessation of cardiac and neurologic activity and function during the dying process and examining the relationship of cardiac activity and function to neurologic activity and function during this same time period.

In order to maximize the unique opportunity of collecting data throughout the dying process from this large prospective study population, we propose to carry out two additional, complementary studies in conjunction with the principal study. The primary objective of Complementary Study 1 is to develop a tool that will help predict the time to death after WLST. Complementary Study 2 will seek to gain insight into the experience of families who are asked to consent to DCD and to having their family member participate in end of life research. For this study, we propose to carry out a nested qualitative study, with the primary objective to describe the experience of surrogate decision makers, as it pertains to the process for consent for organ donation and participation in end of life research. Complementary Study 1 is included in this proposal while Complementary Study 2 will be described in a separate proposal (see Appendix K).

Phase 1 of the DDePICt research program included the completion of a narrative review of the literature focusing on the determination death after cardiac arrest and the associated physiologic changes[8], as well as a systematic review of the published literature regarding the potential for autoresuscitation[9]. In Phase 2, we conducted a multi-centre, self-administered mailed survey of all Canadian critical care physicians. Physicians were asked to describe the current practice for determination of death after cardiac arrest[10]. This survey was funded by a CHEO Research Institute Start-up Grant in 2008. Phase 3 of the program was a multi-centre pilot study to assess feasibility (recruitment, consent rates, and protocol compliance) of collecting epidemiological data on the physiological changes that occur during the dying process and in the post mortem period after cardiac arrest, following WLST[7]. A 2009 CIHR Meeting Grant supported the development of the pilot study protocol and the study itself was jointly funded by grants from the CHEO Research Institute and Physician's Services Incorporated.

A CIHR Meeting Grant that was received in 2012 supported the development of the protocol for the proposed DePPaRT study (phase 4). The Canadian arm of the study itself has already been fully funded as part of the CIHR-funded Canadian National Transplant Research Program (www.cntrp.ca). The Canadian National Transplant Research Program (CNTRP) is a national initiative with 105 investigators and 86 collaborators designed to increase organ and tissue donation in Canada and enhance the survival and quality of life of Canadians who receive transplants. In addition, this proposal and the research program it is part of, has been peer reviewed and endorsed by the Canadian Critical Care Trials Group. The Canadian Critical Care Trials Group (CCCTG) is a national organization of more than 300 individuals with research interests in the management of the critically ill patient with full commitment to ensure that the work is undertaken in a rigorous and ethical manner, and communicated in a timely and effective way. DePPaRT will include an international expansion of the study, to be lead by Dr. Dale Gardiner (United Kingdom), Dr. Paul Shore (United States) and Dr Franki Duska (Czech Republic). Other international collaborations may follow. International collaborators will follow the protocol for the Principal Study (autoresuscitation) and may, choose to opt into the two additional complementary studies (prediction tool and experience of surrogate decision makers) provided the protocols can be satisfied. Funding for international expansion will be by the investigating country.

The results of the proposed DePPaRT study and its international expansion, will lead to development and implementation of national and international standards for the determination of death. Our intention is to inform DCD practice in order to help ensure a safe diagnosis of death after cardiac arrest. The findings of this study will also result in the creation of a more accurate prediction tool for the time to death after WLST. This would allow health care and donation practitioners to identify candidates with a high probability of dying within the current accepted time limit for DCD of 2-3 hours after WLST. Such a tool would minimize resource use and family disappointment if the time of death after WLST was outside the parameters for organ donation.

The findings of the nested qualitative study (Complementary Study 2) will result in a better understanding of the experience of surrogate decision makers who are approached for consent to DCD and who are also part of a research project at this very vulnerable time.

3. RESEARCH QUESTIONS, HYPOTHESES & OBJECTIVES

3.1 Principal Study: Physiologic Function During the Dying Process, following WLST

3.1.1 Research Question:
What is the natural history of cessation of physiological function, after withdrawal of life sustaining therapy (WLST), in adult and pediatric patients?

3.1.2 Hypothesis:
After cessation of cardiac function, identified by absence of pulsation in patients undergoing WLST, cardiac electrical activity may continue for some time but resumption of cardiac or brain function will not occur spontaneously beyond 5 minutes.

3.1.3 Primary Objective:
To determine the incidence of autoresuscitation in critically ill adults and children who die in the intensive care unit (ICU), following WLST. This objective will be accomplished by conducting observational studies in 13 Canadian ICUs (11 adult, 2 pediatric) and 6-10 international collaborating ICUs.

3.1.4 Secondary Objectives:
1. To document the pattern of cessation of cardiac and neurologic activity and function during the dying process and in the post mortem period after cardiac arrest, following WLST.
2. To examine the relationship of cardiac activity and function to neurologic activity and function during the dying process and in the post mortem period after cardiac arrest, following WLST.
3. To determine whether certain specific patient characteristics are associated with different patterns of cessation of cardiac and neurologic activity and functions during the dying process and in the post mortem period after cardiac arrest, following WLST.
4. To determine the value of the lowest arterial blood pressure that is associated with measurable neurologic activity or function.

3.2 Complementary Study 1: Prediction of Time to Death Following WLST

3.2.1 Research Question:
Using readily available information from adult and pediatric patients about to undergo WLST, is it possible to develop a tool that will identify patients who are most likely to die within a time period that permits them to become organ donors?

3.2.2 Hypothesis:
A novel prediction tool for time to death, created using patient specific data collected prior to WLST, will improve identification of patients eligible for DCD.

3.2.3 Primary Objective:
To develop a new reliable tool to predict time to death following WLST in critically ill adults.

3.2.4 Secondary Objectives:
1. To test an existing pediatric tool for the prediction of time to death after WLST.
2. To test the association between a score for a computed tomography (CT) scan of the brain and time to death after WLST in univariate and multivariate analysis.
3. To test the accuracy of previously developed tools and univariate predictors (such as ICU specialist prediction of time to death) for time to death following WLST.

4. BACKGROUND/PRESENT STATE OF KNOWLEDGE/RATIONALE

4.1 General State of Deceased Organ Donation in Canada
Despite Canada's envied health-care system amongst developed nations, we perform very poorly in organ donation. In 2010 the deceased donor rate in Canada was 13.6 donors per million population (PMP)[2] compared to 32 PMP in Spain and 25 PMP in the US, with no improvement in the past decade[2]. The number of transplant candidates has grown each year but the number of deceased donors has not kept pace, leading to more wait-list deaths. In 2010, 16% of kidney-pancreas, 19% of lung, 22% of liver and 24% of heart transplant candidates died on a Canadian wait-list before receiving a transplant[3]. At present, deceased donation occurs by two different methods; following a declaration of death according to: 1) neurologic criteria, NDD or 2) circulatory criteria (DCD). Historically, organ donation after NDD supplied the majority of the organs for transplantation in Canada. Since 2006, DCD has been identified as having the potential to significantly increase deceased donation[11-13]

4.2 Re-emergence of Donation after Circulatory Determination of Death (DCD)
Organ donation after NDD continues to be the dominant source of organs for transplantation. However, because NDD is rare, one of the responses to the mounting supply-demand discrepancy has been the re-emergence of the practice of organ donation after cardiac death or more appropriately referred to as donation after circulatory determination of death (DCD). With NDD, brain death is declared with intact circulation. Organ perfusion (apart from the brain) is maintained with life supporting measures. Conversely, DCD occurs when death is declared after WLST, resulting in cessation of circulation, whereby perfusion of organs, including the brain, is not maintained. With advances in both transplant surgery and organ preservation techniques, the practice of DCD has progressively increased and is common in the United States, Europe and Japan. It now accounts for the largest incremental increase in organ donation in active programs in the UK[14] and US[15,16]. DCD is generally supported by health care professionals and members of the public[17], but it has not been fully embraced by the medical community in Canada, principally for ethical concerns and logistical reasons[18]. In 2011, in Ontario,

DCD accounted for 20% of all deceased organ donors but implementation of programs in the rest of the country remains sporadic[2,11]

There is continuing controversy regarding the criteria used to determine death in DCD practice. Questions regarding the time period required to confirm permanent cessation of cardiac and neurologic function after circulatory arrest, and the potential for autoresuscitation (an unassisted return of spontaneous circulation after a determination of death) persist. Other major barriers to DCD practice include: the uncertainty in predicting which patients will die in a manner allowing them to proceed to successful donation[19]; ethical/legal concerns for using this type of donor[17,20-22]; and relatively low consent rates[23]. The re-emergence of DCD has created the need for further study into current practice for the determination of death following cardiac arrest.

4.3 Cessation of Cardiac Activity and Function During the Dying Process Following WLST

The ethical foundation of deceased donation is the 'dead donor' rule, which states that "vital organs should only be taken from dead subjects and, correlatively, living subjects must not be killed by organ retrieval"[24]. Adhering to this rule necessitates establishing clear evidence and consensus-based medical criteria for determining death. An enormous body of work has been completed over the last several decades to develop such criteria as well as the respective clinical tests required for their fulfillment. However, controversy and variability remain. When we performed a narrative review of international guidelines for the declaration of death, we found and reported wide variability in the criteria used by physicians to determine death after circulatory arrest[8]. In addition, our survey of Canadian critical care physicians demonstrated a similar lack of consensus in choice of clinical criteria for death determination[10].

Most of the concern regarding violation of the dead donor rule within the context of DCD hinges on the variability of the length of the "wait period" required to declare death. In DCD, treatment is withdrawn from the patient, the heart stops beating and following a wait period of 2-10 minutes (depending on the institution and jurisdiction), death is declared and organ retrieval begins. Upon completion of this wait period, an unassisted, spontaneous return of circulation is theoretically no longer possible, thus permanent cessation of circulatory function is confirmed and death is declared. Because of a paucity of data regarding how long this wait period must be, recommendations for its length are based primarily on expert opinion. We conducted a systematic review of the autoresuscitation literature and reported that in the context of a planned WLST, such as occurs prior to DCD following an expected cardiac arrest (also known as Maastricht III DCD[25] and controlled DCD), there were no reported cases of autoresuscitation[26]. This review did demonstrate that in situations where cardiopulmonary resuscitation (CPR) has been attempted but terminated, autoresuscitation has occurred up to 7 minutes following cessation of failed CPR. As well, our survey of intensive care physicians in Canada found that 65% of physicians reported that they believe that autoresuscitation exists and 37% reported that they had personally witnessed autoresuscitation[10]. Other cases of autoresuscitation following failed CPR have been reported. A recent survey of emergency physicians working as part of mobile intensive care units in France also reported that

45% of physicians responding to this survey had personally witnessed a case of autoresuscitation[27]. Greer[28] commented on these findings and added that "Five incidents of autoresuscitation were reported to the United Kingdom National Reporting and Learning System between 2009 and 2011 where the patient's family was prematurely informed of the patient's death after CPR efforts were stopped but the patient survived for a few more hours. In order to prevent this unnecessary distress to families, the United Kingdom, National Patient Safety Agency recently reported this as an emerging risk, and said that it was aware of further similar cases[29]. Improved understanding of the natural history of the dying process after cardiac arrest is crucial to clarify issues of practice and timing of the declaration of death in the context of DCD.[8,10,26,30]

4.4 Cessation of Neurologic Activity During the Dying Process Following WLST
In addition to concerns regarding autoresuscitation, some worry that the wait period for declaration of death is not sufficiently long to ensure that brain function has ceased permanently. In fact, a recent survey of 264 pediatric intensive care physicians reported that only 59.1% agreed or strongly agreed that the time of death in DCD can be conclusively determined and 11.0% agreed or strongly agreed that the pediatric DCD donor may feel pain or suffering during the organ retrieval procedure[31]. Though neurophysiology following cardiac arrest has not been systematically studied in humans, studies have demonstrated that following a cardiac arrest, loss of consciousness and electroencephalogram (EEG) changes (defined as diffuse slowing, suppression or loss) occur within 6.8-20 sec in humans[32-34]. Limited data also suggest that cerebral electrical activity in adults ceases below 50mmHg systolic blood pressure[35] but the minimal duration or pulse pressure needed to sustain or resume perfusion and function of end organs, especially of the brain, is not known. More recent studies have also reported surges of electroencephalographic activity (measured by bispectral index) at the time of death (when there is no discernable blood pressure) in both critically injured but neurologically intact patients[36] and in patients following WLST, awaiting organ donation after cardiac death[37]. Borjigin et al[38] reported similar findings when they performed continuous electroencephalography in rats undergoing experimental cardiac arrest. Their study demonstrated the consistent occurrence of a transient surge of neural correlates of heightened conscious processing within the first 30 s after cardiac arrest, indicating the existence of highly organized brain activity and neurophysiologic features consistent with conscious processing at near death. Given these findings, the collection of data on raw and processed EEGs from many more patients during the dying process after WLST is warranted.

4.5 Prediction of Time to Death Following WLST (Complementary Study 1)
One of the major barriers to DCD is the uncertainty in predicting time to death following WLST. Accurate time to death prediction, as part of donor identification, is crucial for two reasons. First, organ procurement and subsequent donation can only occur if warm ischemia time is limited. Warm ischemia, as defined by the time from WLST to artificial cold perfusion of the retrieved organ, beyond a certain time point (up to 2 hours for lung and kidney but less for liver) irreversibly damages organs and precludes donation[39]. Accurate prediction of time to death after WLST is essential to identify appropriate DCD candidates[19]. If candidates can be accurately identified and health care resources appropriately allocated to DCD donation candidates, financial and health care resource

waste can be minimized. Second, the process of withdrawal can be stressful on both family members and the health care professionals involved in the care of the patient[40], so that an unexpected protracted time to death can be extremely difficult for everyone involved. Furthermore, feelings of frustration and disappointment may be prominent if organ donation is abandoned because of a protracted time to death.

Despite the importance of predicting time to death after WLST, no accurate prediction tool exists. The University of Wisconsin DCD prediction tool[41] has been used by many programs but data has shown that it's predictive value may be suboptimal. Recent Canadian research found that 21% of DCD candidates identified with the Wisconsin tool did not proceed to donation because they did not die within the 2-hour limit. Furthermore, the mean Wisconsin scores were not statistically different between unsuccessful and successful candidates[11]. Current statistics presented to the UK National Organ Donation Committee reported that only 48% of consented DCD patients progress to donation and that the majority of those who do not become donors are because of a prolonged time to asystole[5]. A tool that can be used to reliably predict time to death is needed to allow health care practitioners to focus efforts on candidates with a high probability of dying within a time frame which would allow donation. Such a tool would minimize health care resource waste, reduce family disappointment and optimize organ donation success. One of the complementary studies of DePPaRT will therefore attempt to develop a risk prediction tool to determine time to death after WLST in adults and to validate a preexisting model in children.

In order to inform data collection for the DePPaRT study, a systematic review was performed to determine the risk factors/ risk prediction models/clinical decision tools for patients who undergo withdrawal of life sustaining therapy (including potential DCD candidates) that are associated with and/or predict time to death (see Appendix C for details). In total, 13 full text articles met our pre-specified inclusion criteria, of which seven developed/and or validated a prediction tool and four evaluated risk factors associated with time to death after WLST. Of particular interest, Brieva et al performed a multi-centre study of 765 adult patients undergoing WLST in Australia and reported that ICU specialist opinion was the best individual predictor of time to death within 60 minutes, with an accuracy of 0.80 (0.75–0.83) in development and 0.78 (0.74–0.82) in their test set[42]. While promising, these results require further validation. With respect to prediction of time to death in the pediatric population, Shore et al have developed a tool that they describe as being a reasonable preliminary predictor for death within 30 or 60 minutes after withdrawal of support in terminally ill or injured children, but that prospective validation of this tool is required[43]

Based on the findings of our systematic review, a number of risk factors were shown to be significantly associated with the time to death after WLST. The following risk factors were found in multiple studies to be significantly associated with time to death after WLST in multivariable analysis: Age, Body Mass Index, airway type (endotracheal tube versus tracheostomy), mode of mechanical ventilation, ventilator parameters, inotrope and vasopressor use, extracorporeal membrane oxygenation and ventricular assist device

use. Several other risk factors were also found to be statistically significant in single studies only. The above-mentioned study by Brieva et al was the only one to demonstrate that ICU specialist opinion was an accurate predictor of time to death within 60 minutes following WLST.

4.6 DDePICt Pilot Study

Prior to embarking on a large observational study of the natural history of cessation of physiological function after cardiac arrest, following WLST (the DePPaRT study), we felt it prudent to conduct a feasibility study. We completed a pilot observational study (n=41, from 5 centres, 4 adult/1 pediatric (see Appendix B) that examined the physiological changes that occur during the dying process and in the post mortem period after cardiac arrest. Vital sign data was collected from 33/41 patients (30 adult/3 pediatric). Electroencephalogram (EEG) waveforms were also collected on 4 of these 33 patients. The results from this study demonstrated that it is feasible (91% (41/45) recruitment rate, 87% consent rate, 76% protocol compliance) to study the natural history of death by describing vital signs during the dying process and 30 minutes after declaration of death and that physiological data such as arterial waveforms could be successfully recorded and analyzed. We also concluded that a larger study is needed to support the following preliminary findings: 1) no return of circulation occurred after 89 seconds of cessation of arterial blood pressure activity (which is consistent with current practices for determining death prior to controlled DCD) and 2) that persisting electrocardiogram activity, in the absence of circulation, does not appear to have obvious clinical relevance to declaration of death for DCD.

4.7 Summary Rationale For a Multicentre International Observational Study

For DCD to proceed in a broader environment, the criteria pertaining to permanent cessation of neurologic and cardiac function after cardiac arrest need to be clarified. Questions of whether the wait time periods of current DCD protocols are adequate to ensure that donors are dead prior to organ retrieval need to be addressed. To date, there has been no rigorous attempt to resolve the uncertainty of how long one should wait to determine death following a cardiac arrest to ensure a safe diagnosis of death and yet be able to maintain organ viability but results from our pilot study demonstrate that such a study is indeed feasible. Without clarity, current DCD protocols in Canada and internationally may be perceived to violate the “dead donor rule” and compromise patient welfare. In addition, predicting the time to death to less than 2-3 hours after WLST is crucial for successful organ donation outcomes and to avoid further emotional distress for families and the treating healthcare team [44,45]. The UK Donation Ethics Committee and a consensus meeting between the UK Intensive Care Society and British Transplantation Society have both identified the need to develop a scoring system to help predict the liklihood of death within a given time period, which would save families considerable distress by identifying patients who would not be suitable for DCD[46,47].

Without more research on the dying process and death determination, DCD practice in Canada and internationally will remain sporadic, with the loss of potential donors and loss of end of life autonomy for persons who have in life registered the wish to be an

organ donor. A multicentre, prospective, observational study of the physiologic changes that occur during the dying process, following WLST, in intensive care patients, will address the above mentioned concerns by: 1) providing information on the disappearance and possible reappearance of key circulatory and neurologic measures; 2) producing an accurate tool for the prediction of time to death and 3) describing the experience of surrogate decision makers in deciding whether to consent to DCD and participate in research at the end of life (for the nested qualitative study protocol, see Appendix K).

5. RESEARCH DESIGN/METHODS/ANALYSIS

5.1 Study Design

A multi-centre, prospective, observational, longitudinal cohort design will be used. A staggered start will be used to enroll a total of 500 patients from 13 Canadian sites (11 adult, 2 pediatric ICUs, see Appendix A for site details) over a period of 30 months.

5.1.1 Study Population

Inclusion criteria:

- Admission to the intensive care unit
- Age $\geq$ 1 month
- Situation in which a consensual decision to WLST has been made and there is an anticipation of imminent death
- Subjects will have a *minimum* of the following bedside monitors in place:
    i. Pulse oximeter plethysmography
    ii. Continuous 3-lead electrocardiogram
    iii. Invasive arterial blood pressure monitoring

[Please note that at all centers, data will be collected from the end-tidal CO_2 capnogram, if in place already. In addition, at specific centers having the capability for continuous neurologic monitoring, data will be collected from the electroencephalogram. Having these monitors in place is NOT part of the inclusion criteria]

Exclusion criteria

- Declared dead by NDD criteria
- ICU Physician or member of the bedside healthcare team refusal
- Surrogate decision maker or legal guardian refusal or unavailable to obtain consent
- Functioning pacemaker

A Purposive Sampling Strategy will be used to recruit patients meeting the above inclusion/exclusion criteria from the following groups (Figure 1). A total of 500 patients will be recruited. Maximum amounts can be recruited in each group, however, when 500 patients are enrolled, recruitment will end.

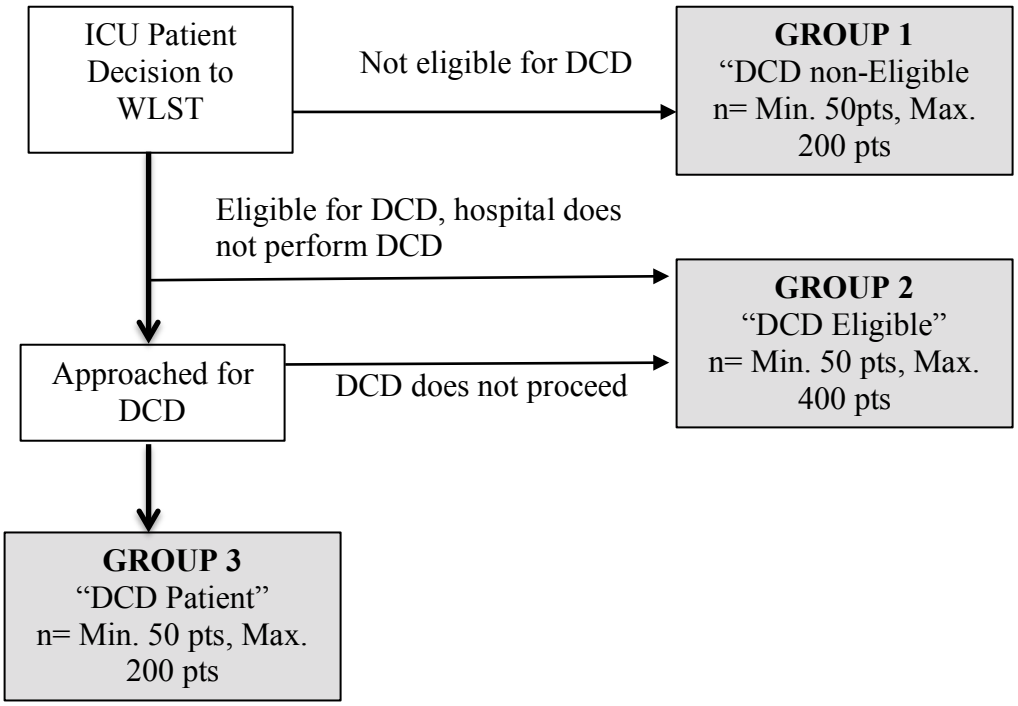
1. GROUP 1: "DCD non-eligible" patients (Minimum 50, Maximum 200 patients):

Any patients who fulfill study inclusion and exclusion criteria but who did not meet criteria to be considered eligible to be DCD donors.

2. GROUP 2: "DCD Eligible" patients (Minimum 50, Maximum 400 patients): Patients who were:
    a. consented to DCD but did not proceed to donation or
    b. met criteria to be DCD donors but consent was refused or
    c. met criteria to be DCD donors but were treated in a centre that does not perform DCD
3. GROUP 3: "DCD patients" (Minimum 50, Maximum 200 patients): Patients who met criteria, had consented to be DCD donors and whose organs were recovered.

As an example, if 100 patients are recruited from Group 1, and 350 patients recruited from Group 2, the remaining 50 patients would have to be recruited from Group 3.

Figure 1: Purposive Sampling: Total Sample Size n = 500 patients



GROUP 1&2 - monitored 15 minutes prior to WLST until 30 minutes after declaration of death.
GROUP 3 - monitored 15 minutes prior to WLST until removal of organs.

Eligibility for DCD will be assessed during the screening process, using the criteria outlined for provincial and national recommendations for DCD [48,49]. Absolute contraindications to DCD are as per Blackstock et al 2013[50] (see Appendix D for detailed eligibility criteria).

Population Rationale

The population will exclude the neonatal population, typically thought to have unique physiology, differing withdrawal of life support practices, and ethical challenges that should require separate evaluation. As well, subjects who have consented for organ donation by NDD will be excluded since death is already declared using neurologic rather than circulatory criteria.

The target patient population to study the physiology and natural history of cardiac and neurologic function after WLST and 30 minutes after declaration of death includes any patient who fulfills the above inclusion/exclusion criteria. However, since Complementary Study 1 is designed to develop a tool for the prediction of time to death within 2 hours, as a means of improving the identification process for DCD candidates, for Complementary Study 1, the target population will include ONLY patients who fulfill the inclusion/exclusion criteria AND who are either DCD donors or who fulfill DCD eligibility criteria but do not become donors (Groups 3 and 2, see Figure 1 above). In order to have a sufficient sample size for Complementary Study 1, we aim to recruit patients such that those in Groups 2&3 combined account for at least 60% of the total sample. However, we anticipate that recruitment of patients from Group 1 will occur faster than from Groups 2&3. In order to limit Group 1 to 40% of the total, an interim analysis will be performed for each site at the end of the first year of the study. There is an acknowledgement that actual DCD patients are rare. The surrogate DCD-eligible (Group 2) will have similar characteristics. Recruitment of DCD-eligible patients will be more common, especially given that some of the study sites do not yet practice organ recovery by DCD. DCD non-eligible (Group 1) patients have been included to ensure a large enough cohort to examine the primary objective (autoresuscitation) in a timely period.

5.2 Methods

5.2.1 Subject Recruitment

- A member of the treating team will obtain permission from the surrogate decision maker to be approached by the research coordinator to discuss participation in the research study.

- For the adult sites, the attending physician and the site investigator will *not* be involved in obtaining consent. The research coordinator will obtain informed consent as per ICH Guidelines (see Appendix E for Consent Form). At the pediatric sites, the attending physician will obtain informed consent as required by the CHEO REB for the pilot study (see Appendix B).

5.2.2 Study Procedures

- Once enrolled in the study, subjects will continue to be monitored by the bedside monitors that are in place. Waveform data will be transferred to the central monitor and monitors will be left on for up to 30 minutes after the clinical determination of death. Staff may leave the bedside screen on or turn it off, as per institutional local practice.

- At the end of the data collection period, the research coordinator will electronically transfer all the de-identified waveform data for the period of time from at least 15 minutes prior to WLST until the end of the data collection period (see Appendix F, Figure 1), to a custom made, password protected secure website (See Appendix G for detailed description of the process of electronic data capture, transfer and analysis). If death has not occurred and does not appear imminent 24 hours after WLST, or if transfer out of intensive care for ongoing end of life care has occurred, collection of electronic waveform data will be stopped. The patient's data collected up to this point will be included for analysis.

- At specific, pre-identified study sites, at the time of enrollment, the research coordinator will ask the surrogate decision maker who was approached concerning organ donation, if they would be willing to be contacted in six months to be part of a qualitative study designed to investigate their experience with organ donation and end of life research. (See separate submission for the protocol for the study, "Understanding the experience of DePPaRT families with end-of-life decision-making, and decision-making about organ donation and research participation") (see Appendix K).

- Physiologic waveform data will be collected privately and confidentially. ICU staff and patient's family will be blinded from data collected to prevent intervention. That is, the research coordinator will not inform the ICU staff (nurse, inhalation therapist, nor physician) or the subject's family of any clinical findings during the study procedures. As previously described, the expected incidence of autoresuscitation is low. However, if autoresuscitation did occur, staff response would be as per institutional local practice.

- The patient's family will be able to be with the patient throughout the study procedures as per local practice and there will be no restrictions on their activities at the bedside as a result of the patient's participation in the study. There will not be any other interventions or change in care of the patient as a result of participating in this study. The research coordinator will not participate in any aspect of end of life care.

- Given that families will be dealing with an extremely stressful situation, if required, they will be supported in the most appropriate means necessary (i.e. using palliative care, social services, pastoral care, etc.) throughout the study process to address their concerns and help them to cope.

- If, the monitoring equipment (i.e. ECG leads, probes etc..) is detached at the request of staff or surrogates or for the purpose of organ recovery, the subject will not be excluded from analysis with monitored data being analyzed up to that point in time.

- Descriptive data of procedure, medications, and interventions will be collected before, during, and after WLST up until the declaration of death.

5.3 Outcome Measures

5.3.1 Principal Study (Physiologic Function During the Dying Process Following WLST)

Primary Outcome

- The primary binary outcome variable will be the incidence of autoresuscitation.
- For the purposes of this study, autoresuscitation is defined as an unassisted return of spontaneous circulation (ROSC) after a determination of death.
- ROSC is defined as one or more of the following signs: heart sounds by auscultation, pulse (detected by palpation or doppler), blood pressure (detected by invasive or non-invasive methods), oxygenation (detected by pulse oximetry), and resumption of breathing or other neurologic function (detected by EEG or clinical observation).

Secondary Outcomes

- Secondary outcomes will include the disappearance and any reappearance of cardiac and neurologic activity and function. These outcomes will be determined by recordings time points from the following:
    a. Pulse oximeter plethysmography
    b. 3 lead Electrocardiogram (ECG)
    c. Invasive arterial blood pressure
    d. End-tidal CO_2 capnogram (**when available**)
    e. Full array (10-20 International Electrode Placement) Electroencephalogram (EEG, **when available**).

5.3.2 Complementary Study 1 (Prediction of Time to Death Following WLST)

Primary Outcome

- The primary binary outcome variable will be death within two hours following WLST in adults.
- Time to death will be defined as the time between the initiation of WLST, as defined by the first act of extubation, cessation or weaning of vasopressors or

weaning of the ventilator settings, and cessation of invasive arterial blood pressure waveform for five minutes.

Secondary Outcomes

- The secondary binary outcome variable will be death within one hour following WLST in adults.
- Time to death will be defined as above.

5.4 Data Collection and Management

5.4.1 General Information Variables

The following data will be abstracted and recorded onto a paper Case Report Form (CRF, see Appendix H) and then entered into an electronic database on a secure website:

- Baseline demographics (including age, sex, Body Mass Index), hospital length of stay, ICU length of stay, diagnosis (including intracranial injury etiology), underlying disease, co-morbidities (cardiovascular, pulmonary, neurological, hematological, malignancy, gastroenterological) and APACHE II score for adults or PRISM III score for pediatrics.
- Organ donor status – the eligibility of the patient, approach and consent by surrogate decision makers will be documented
- All interventions and medications (sedatives, analgesics, inotropes and vasopressors) including type and doses administered or stopped immediately prior to and during the WLST.
- Oxygenation and ventilation modes and changes prior to and during WLST.
- The time of initiation of the WLST and the time of clinical declaration of death as deemed by the ICU staff, as well as any observed instances of resumption of respiratory, circulatory, or neurologic activity.

5.4.2 Variables Specific to the Principal Study (Physiologic Function during the Dying Process Following WLST) only

The following physiological waveforms will be collected from at least 15 minutes prior to the WLST until up to 30 minutes (depending on study subject and site) after the declaration of death:

- Pulse oximeter plethysmography
- Electrocardiogram (ECG)
- Arterial Blood Pressure (ABP)
- End-tidal CO_2 capnogram (at specific sites)
- Electroencephalogram (at specific sites)

All de-identified vital sign waveform data will be electronically retrieved from bedside monitors via the central station and uploaded onto a secure website. The electronic data capture system developed will provide comprehensive beat to beat waveform data collection with online, remote reviewing of de-identified patient data

that will not interfere with local hospital data collection practice/procedures. **(**See Appendix G for detailed description of the process of electronic data capture, transfer and analysis).

5.4.3 Variables Specific to Complementary Study 1 (Prediction of Time to Death following WLST)

The following data will be collected from the chart as close to the time of WLST as possible. It will be recorded onto a paper CRF and then entered into a database on a secure website:

Cardio-Respiratory Variables

- Airway type, defined as ventilation or respiration through either an endotracheal tube, tracheostomy tube a non-invasive mask or naturally.
- Ventilator type, will either be through a conventional ventilator or non-conventional ventilator (high frequency oscillator, jet ventilator, extracorporeal membrane oxygenator).
- Ventilator settings (mode of ventilation, FiO2, pressure support - positive end expiratory pressure, mean airway pressure, peak inspiratory pressure)
- Spontaneous respiratory rate (presence will be defined as a respiratory rate on a ventilator greater than the set rate if on a controlled mode or any spontaneous mode), tidal volume, oxygen saturation (SaO_2), blood pressure, heart rate, blood gases (PaO_2, $PaCO_2$) and blood pH (arterial gases will be used for blood gas data, but if not available venous gases will be substituted for pH and $PaCO_2$)
- Cardiac support device (aortic balloon pump, ventricular assist device, extracorporeal membrane oxygenator)
- Withdrawal to room air or to oxygen will also be collected as well as withdrawal with extubation of endotracheal tube, or tracheostomy. Use of airway devices (nasal airway, oral airway) during the withdrawal process will also be documented. We will also collect data on whether all supports were withdrawn immediately or sequentially.

Neurologic Variables

- Glasgow Coma Scale Score and breakdown, presence or absence of brain and brainstem reflexes (corneal reflex, pupillary light reflex, cough/gag reflex, motor response), intracranial injury etiology,
- CT results (CT Scan (Head) and Marshall Score))

Other

- ICU physician and bedside nurse prediction of time to death

5.5 Statistical and Data Analysis

5.5.1 Sample Size

Principal Study (Physiologic Function During the Dying Process Following WLST)
Primary Outcome –Incidence of Autoresuscitation:
Given that we expect the incidence of autoresuscitation in a controlled setting (i.e. following WLST) to be at most extremely low[9,26,51,52], its precise estimation is difficult without an extremely large sample size. In such cases the 'rule of three'[53] can be used as means of determining a practical sample size. If none of n patients show the event of interest, we can be 95% confident that the chance of this event is at most 3/n. Thus, we have chosen a sample size of 500 participants as reasonable to achieve our objectives with acceptable precision. If we do not find any cases in 500 patients then the risk of autoresuscitation is <1%. In our pilot study, recruitment was capped at 10 patients for the adult sites and 5 patients for the pediatric site. We recruited a total of 41 patients with two sites achieving this at 6 and 8 months respectively. With the addition of 8 high volume sites and the inclusion of DCD patients for the current study, we expect to recruit approximately 20 patients/month. We therefore estimate that it will take approximately 2 years to recruit 500 study subjects (20 pediatric, 480 adult) from 13 Canadian study sites. Our proposed sample will be by far the largest and the only prospective analysis on this topic to date.

Complementary Study 1 (Prediction of Time to Death Following WLST)
Primary Outcome - Time to Death: In order to develop a prediction tool for time to death after WLST, we use a subgroup of patients from the original cohort for the principal study (see "Study Population" for details). This subgroup will include only those patients who will either be organ donors (Group 3) or who meet criteria for organ donation (Group 2). As the prediction tool is meant primarily to determine organ donation candidacy, the study population will need to be made up of that target population. Due to the purposive sampling, of the 500 patients being sampled for the primary objective of the principal study, approximately 300 will meet criteria to be in Group 3 or Group 2. Data from the pilot study demonstrated that 60% of patients died within two hours of WLST[7]. Given these estimates we will collect data on 180 patients who will have had the outcome of interest. Based on a commonly accepted rule of thumb in regression modeling that ten events (patients with outcome) per variable are needed to have acceptable Type I and Type II error, we will be able to include roughly 18 variables in our model. This will be acceptable to develop our new prediction tool.

We also plan to examine the validity of a pediatric prediction tool by Shore et al[43]. Based on the pilot data we plan on recruiting 20 pediatric patients (4-5 patients per year x 2 years x 2 sites). Although this number will be too small to externally validate Shore's model, we will be able to test the model performance in a pediatric population.

International Collaboration: Additional patients from 6-10 international sites will increase the total sample. The international protocol will be consistent with the Canadian

protocol to ensure homogeneity of the sample population and possible pooling of the data.

5.5.2 Analysis

Principal Study (Physiologic Function During the Dying Process Following WLST)
All statistical analyses will be performed using SPSS (version 21). Demographic and physiological characteristics of persons participating and not participating in the study will be presented. For categorical variables, frequencies and percentages will be tabulated. For continuous variables, means, medians, standard deviations, interquartile ranges, maximum, and minimum will be tabulated. Associations between variables will also be examined. Descriptive statistics for the primary outcome measure, the incidence and timing associated with the return of key circulatory measures, will be created.

An adjudication committee of 10 physicians who are not part of the study will be formed. Tracings from each subject will be reviewed by at least 2 adjudicators to determine cessation and resumption of activity. A third adjudicator will resolve any discrepancies. If needed for consensus, the primary study investigator (S Dhanani) will act as a fourth adjudicator. Data from the reviews will be entered into a database on a customized website, as described above (See Appendix H for Adjudication instructions and data collection tool).

Complementary Study 1 (Prediction of Time to Death Following WLST)
Descriptive analyses of the collected variables will be performed. We will explore all variables with frequency distributions. For normally distributed continuous data, results will be expressed as means ± standard deviations. For skewed continuous data, results will be expressed as medians ± interquartile ranges. Categorical variables will be expressed as proportions. The distributions of all variables will be explored in patients with and without the primary outcome.

Model development: logistic regression analysis will be used to develop the prediction model. Due to the constrained number of events per variable, candidate variables will be chosen based on 1) strength of association with outcome as defined by the current evidence in the literature and 2) strength of association as demonstrated on a univariate analysis 3) completeness of data collection and 4) consideration of whether the same concept will be better captured by alternative variables. Variables associated with time to death in a univariate analysis with a p-value of less than 0.1 will be passed on to the multivariable stage. All variables will be categorized into groups to best reflect either 1) important categorical cut offs already defined in the literature or 2) clinically commonly employed cut offs. For ease of clinical use, continuous data will also be categorized.

All candidate variables will be entered simultaneously into the model, followed by a backwards stepwise selection process, with the least statistically significant variable being removed. At each stage, model discrimination will be assessed with the c index, equivalent to the area under the receiver operating characteristic curve, and the Brier's score, the mean squared error between outcome and prediction. Model calibration will be performed by graphical plots of observed versus expected risk. In order to adjust for optimism, Efron's Bootstrap analysis will be used to calculate an adjusted C index and

Briers score. The model will be chosen to best balance parsimony and model performance. Robust standard errors will be used to allow for clustering within critical care units.

Missing data: In order to minimize missing data we will try to minimize losses to follow up, use database macros to avoid data entry error, and ensure thorough cleaning of the data set. Missing data will be managed using the multiple imputation technique. Multiple imputation aims to approximate the distributional relationship between the missing data and available information through a multistep modeling process[54]. The first step will be identifying missing data and discerning the possible underlying mechanisms for the missing data. Imputation models will then be created with predictor variables that will be selected based on literature review, expert opinion and data analyses. Multiple imputed datasets will then analyzed and combined. The results will be presented with and without the imputed data.

Statistical analyses will be performed using Stata Version 10.1 (StataCorp LP, College Station TX).

STUDY MANAGEMENT

6.1 Personnel

This study, conducted in as part of the Canadian National Transplant Research Program and endorsed by the Canadian Critical Care Trials Group, is a collaboration of the Clinical Research Unit at the Children's Hospital of Eastern Ontario Research Institute, the Bertram Loeb Research Consortium (a multi-disciplinary research group based in the Faculty of Arts at the University of Ottawa), the McGill University Health Centre and the Ottawa Health Research Institute. The Canadian National Transplant Research Program (www.cntrp.ca) is a national program of research led by Drs. Lori West and Marie-Josée Hébert bringing together 105 researchers and 86 collaborators from across Canada to conduct research on donation and transplantation in Canada. CIHR funding and support for the program was announced publicly in the spring of 2013. The Canadian Critical Care Trials Group is a multi-disciplinary, national research consortium with a strong commitment to advancing the care and improving the outcomes of critically ill patients through excellence in clinical research.

The principal investigator and co-investigators, together with the project lead, central research coordinator and administrator, will be responsible for the overall supervision of the study. The day-to-day management and administrative support of the study will be the responsibility of the central research coordinator. The lead project manager will support the central research coordinator as needed.

The Children's Hospital of Eastern Ontario and Ottawa Hospital Research Institutes will oversee data management. The study site research coordinators and investigators will be responsible for screening patients, obtaining consent, and training of ICU nurses to perform the collection of data. The principal investigator and co-investigators will review compliance with the study protocol and recruitment rates on a monthly basis.

International collaborators will assign their own personnel as per local arrangements. The Canadian investigating team will retain overarching responsibility for the study and

carry out the data analysis.

6.2 Patient Screening and Enrolment

All patients in the ICU will be screened daily (excluding weekends and holidays) for eligibility. Eligible patients will be identified by the site investigator or delegate who will then notify the site research coordinator. The research coordinator will not be in any way responsible for the care of the patient while in the ICU. Only after the surrogate decision maker of the patient meeting the inclusion criteria has given consent to WLST and DCD (in sites where DCD is practiced), will the site investigator or delegate ask permission for the site research coordinator to approach them to discuss the possibility of having the patient participate in the research study. The attending physician will not be involved in obtaining consent, unless stipulated by the institutional Research Ethics Board. The site research coordinator will obtain informed consent as per ICH Guidelines. Documentation of this process will be noted in the patient's medical chart.

Each site will be provided with patient identification numbers. Patient identification numbers will be assigned sequentially when a patient is enrolled and will be used in all study documentation. The site research coordinator will notify the central coordinator at the coordinating centre of patient enrolment with the assigned patient's identification number. Data on all potentially eligible patients will be recorded on a screening log. Reasons for non-enrolment will be recorded. The screening log will be forwarded to the lead project coordinator on a monthly basis.

7. RISKS/ETHICAL CONSIDERATIONS

There are no assumed risks associated with the proposed assessment procedures. No issues were identified during the pilot study exemplified by high consent rates, and the majority of staff involved in bedside care during the study felt that they were comfortable treating the patient during the study collection period (see Appendix B). ICU staff involved in decision making for WLST will not participate in the consent process for this study. ICU staff will be blinded to the data collection, preventing active intervention based on study results. The research coordinator will not participate in local WLST practice. Routine end of life care will not be affected.

We will not record any patient identifying information on the Case Report Form; a unique study number will identify patients. All study information will be stored in a secure location. The database will not contain personal information that could identify patients. Due to the need to centralize data analysis, the need to work with large data files, and the need for a standardized approach at different centers, a web-enabled DePPaRT domain will be created. Along with clinical data using secure electronic Case Report Forms, the waveform data files will be compressed and uploaded to a central secure website for data storage and variability analysis. As done for previous studies, the website will be built with automated data back-up and all uploaded data will be de-identified and password protected[55,56] (see Appendix F). This system will provide comprehensive beat to beat waveform data collection with online, remote reviewing of de-identified patient data that will not interfere with local hospital data collection

practice/procedures. No identifying information will be used in the publication of study results. All data will be destroyed 7 years after completion of the study.

If required, families will be supported in the most appropriate means necessary (i.e. using palliative care, social services, pastoral care, etc.) throughout the study process to address their concerns and help them to cope. The study protocol will be submitted for ethics approval to the Research Ethics Board of the individual hospital sites with assistance from the lead coordinator. A consent form has been developed with contributions from bioethics and a legal representative (see Appendix E).

8. DISSEMINATION OF RESULTS

The results of this study will be presented at international meetings and national meetings of the Canadian Critical Care Trials Group, the Canadian Critical Care Society and Canadian Critical Care Forum, the Canadian Society of Transplantation and the Canadian National Transplant Research Program. The study results will be submitted for publication to high impact journals once complete. We will also present these findings, within the context of DCD, to the provincial Organ Procurement Organizations and Canadian Blood Services. International collaborators will present to their respective national bodies.

9. STUDY MILESTONES

YEAR 1
First Six Months

- REB approval at primary study site (CHEO)
- Study Procedure Training at CHEO
- Development of Website and process for Electronic Data Capture
- REB approval at all other sites

Last Six Months

- Study Procedure Training at all sites
- Initiation of patient recruitment and data collection at CHEO first and then staggered start for all sites

YEAR 2
First Six Months

- Study Procedure Training and Electronic Data Capture Process at any sites that were delayed
- Initiation of patient recruitment and data collection at delayed sites

Last Six Months

- Continuation of patient recruitment and data collection at all sites

YEAR 3

First Six Months

- Continuation of patient recruitment and data collection at all sites

Last Six Months

- Completion of patient recruitment and data collection at all sites
- Data analysis for principal and complimentary study

10. IMPACT

Despite recurring calls for more research to investigate the question of autoresuscitation, a large, prospective, observational study of the clinical determinants of death and irreversibility after cardiac arrest has never been undertaken. Perceived violation of the dead donor rule, putting practitioners at risk of being accused of causing the death of a patient for the purposes of organ donation, is of major concern. Further, the inability to predict with more certainty time to death after WLST continues to complicate the decision to move forward with donation because of cost of care and impact to the family. The re-emergence of DCD programs is currently hindered by the aforementioned ethical and legal concerns. This study is supported by provincial and national organizations including the Canadian Critical Care Society (see Appendix I).

The proposed study will provide much needed data for use in addressing the physiological and ethical concerns about DCD program development and help establish accepted medical practices and public health policy for death after cardiac arrest. A prospective observational study of the natural history of cessation of physiological function after WLST will provide clarity and certainty in the determination of death within the DCD context. The results are expected to be generalizable to end of life care practice for all adult and pediatric patients. A safe diagnosis of death is important regardless of the context. Development of a tool that would help identify patients best served by organ donation would not only be cost effective but would offer benefit to patients, families and caregivers.

11. RELEVANCE TO CHILD HEALTH

The public and our governments support donation and DCD practice, but advances in technology, donation and transplantation have clouded the lines between life and death necessitating clarity on when death has occurred. Resolving this issue is critical to expanding DCD practice. In particular, because the potential for donation in children is less, DCD has made a great impact by increasing the potential pool for donation in children. Patient safety and public trust in organ donation rely on clear parameters of practice, especially for pediatrics. Public health policies around death and eligibility for donation should not be confounded by uncertainties. This is the first multicentre study to systematically collect information on the physiologic determinants of death after cardiac arrest in a relatively large number of pediatric patients. The results from this study will contribute to the establishment of accepted medical practices for cardiac death in children and will inform clinical practice, DCD program development and public health policy.

12. FUTURE DIRECTIONS

The proposed DePPaRT study (phase 4) will provide further sound scientific basis for the safe determination of death in general and will lead to the development and implementation of robust standards for the determination of death in the context of DCD, in Canada and internationally. These standards will either lend strong support for existing national and international DCD recommendations or provide suggestions for modifications based on empirical evidence. In conjunction with the currently proposed study, specific members of our Steering Committee will be conducting basic research using an animal model to explore the changes that occur in brainstem function following cardiac arrest. Such changes may not able to be studied in dying patients because of serious ethical concerns raised by their overly invasive nature. Addressing these concerns will have medical, ethical, and legal implications and support the development of DCD programs.

13. BUDGET AND JUSTIFICATION
(See Appendix J for further details on justification)

DePPaRT STUDY	Year 1	Year 2	Year 3	Total
PERSONNEL				
Project Coordinator (0.32, 0.32, 0.2 FTE@$40/hr+ 23% benefits + 5% increase per year)	$30,701	$32,236	$21,106	$ 84,043
Critical Care Clinical Research Coordinator (1.0, 1.0, 0.5 FTE@$35/hr+ 23% benefits + 5% increase per year)	$83,948	$88,744	$46,771	$219,463
Biomedical Engineer, PhD - supervise monitoring data collection (0.2, 0.12 FTE, @ $32.5/hr + 26% benefits + 5% increase per year)	$15,970	$10,025	$-	$25,995
Biomedical Engineer, MSc - enable, coordinate monitoring data collection (1.0, 0.65 FTE, @ $28/hr + 26% benefits + 5% increase per year)	$68,796	$47,355	$-	$116,151
Site Research Coordinators - Start up costs ($3000 per site) x 13 sites+ 23% benefits + 5% increase per year	$47,970	$-	$-	$47,970
Site Research Coordinators - Patient Screening/Enrolment (2 hrs/pt @ $35/hr + 23% benefits+ 5% increase per year)	$11,882	$25,213	$13,240	$50,334
Site Research Coordinators ($250/pt x 500 patients+ 23% benefits+ 5% increase per year)	$38,438	$76,875	$38,437	$153,750
Database Set up (includes statistical review & validation) ($35/hr x 60 hrs+ 23% benefits)	$2,583	$-	$-	$2,583
Statistician ($75/hr x 30 hrs YR1 and 100 hrs YR3 + 26 %)	In Kind ($2,835)	$-	In Kind ($9,450)	In Kind ($12,285)
TOTAL PERSONNEL	**$300,287**	**$281,357**	**$120,034**	**$701,678**
PROFESSIONAL SERVICES & SUPPLIES				
Services				
Website design - $75/hr x 4 wks x 37.5 hrs/wk	$11,250	$-	$-	$11,250
Website maintenance (1 hr/wk @ $75/hr x 52 wks)	$-	$3,900	$3,900	$7,800
Translation of consent form (0.30 cents/word @ 2500 words)	$750	$-	$-	$750
Courier	$800	$800	$800	$2,400
Printing/Copying	$500	$500	$500	$1,500
Teleconference costs (teleconference meetings - quarterly) - Steering Committee	$800	$800	$800	$2,400
Teleconference costs (teleconference meetings with sites for establishing collection of monitoring data)	$150	$150	$-	$300
Total Services	**$14,250**	**$7,150**	**$6,500**	**$27,900**
Supplies				
Office Supplies	$800	$500	$300	$1,600
TOTAL PROFESSIONAL SERVICES AND SUPPLIES	**$15,050**	**$7,650**	**$6,800**	**$29,500**
TRAVEL				
Travel to sites for training (average $3,000 per site)	$30,000	$-	$3,000	$33,000
Travel to sites for IS development (average $1,500 per site)	$15,000	$-	$-	$15,000
TOTAL TRAVEL	**$45,000**	**$-**	**$3,000**	**$48,000**
TOTAL BUDGET	**$360,337**	**$289,007**	**$129,834**	**$779,178**

14. APPENDICES

14.1 APPENDIX A
STUDY MEMBERS

1. PRIMARY INVESTIGATOR – Sonny Dhanani
2. STEERING COMMITTEE, CO-INVESTIGATORS

Name	Credentials	Institution	Role	Contact
Jane Chamber-Evans	N, M.Sc. A., M.Sc. (Bioethics)	McGill University Health Centre	Advisor, Ethics, Co-Investigator, Complementary Study 2	Jane.evans@videotron.ca
Jennifer Chandler	LL.M., LL.B., B.Sc.	University of Ottawa	Lead Investigator, Complementary Study 2	jennifer.chandler@uottawa.ca
Dale Gardiner	MBBS, FANZCA, FRCA, BIOETH	Adult Intensive Care Unit, Queen's Medical Centre	International Collaborator	dalegardiner@doctors.org.uk
Teneille Gofton	MD, FRCPC	London Health Sciences Centre	Advisor, Neurology, and Site Investigator	teneille.gofton@lhsc.on.ca
Laura Hornby	M.Sc.	Children's Hospital of Eastern Ontario, University of Ottawa	Lead Project Manager	lhornby@uottawa.ca
Greg Knoll	MD, M.Sc., FRCPC	Ottawa Hospital Research Institute, University of Ottawa	Senior Advisor, Organ Donation	gknoll@Ottawahospital.on.ca
Maureen Meade	MD, M.Sc.	Professor, Departments of Medicine and Epidemiology & Biostatistics, McMaster University Research Director, Critical Care, Hamilton Health	Senior Methodology Advisor	meadema@hhsc.ca

		Sciences Critical Care Consultant, Hamilton Health Sciences		
Tim Ramsay	Ph.D.	Ottawa Hospital Research Institute	Advisor, Statistical Analysis/Study Methodology	tramsay@ohri.ca
Andrew Seely	MD, Ph.D., FRCSC	The Ottawa Hospital-General Campus	Advisor, Information Technology, and Site Investigator	aseely@ohri.ca
Jason Shahin	MDCM, FRCPC, M.Sc.	McGill University Health Centre	Lead Investigator, Complementary Study 1,and Site Investigator	jason.shahin@mcgill.ca
Sam Shemie	M.D., FRCPC	Montreal Children's Hospital, McGill University Health Centre, McGill University, University of Ottawa, Canadian Blood Services	Senior Advisor, Death Determination, Organ Donation	sam.shemie@mcgill.ca
Amanda van Beinum	M.Sc.	Children's Hospital of Eastern Ontario	Central Research Coordinator	avanbeinum@cheo.on.ca

3. ADMINISTRATOR

- Paulina Mirsky – Loeb Research Consortium

4. COLLABORATORS

a. Study Sites and Site Investigators:

St Michael's Hospital, Toronto - Site for Qualitative Interviews
Andrew Baker, MD – bakera@smh.ca
Jan Friedrich, MD – friedrichj@smh.ca

Queen Elizabeth II Health Sciences Centre, Halifax
Stephen Beed, MD – stephen.beed@dal.ca

Foothills Medical Centre, Calgary – Expertise in Neurologic Assessments
Christopher J (Chip) Doig, MD – cdoig@ucalgary.ca

Hospital for Sick Children, Toronto– Expertise in Neurologic Assessments
Anne Marie Guerguerian, MD – anne-marie.guerguerian@sickkids.ca

McGill University Health Center, Montreal - Site for Qualitative Interviews
Jason Shahin – jason.shahin@mcgill.ca
Sunnybrook Hospital, Toronto - Site for Qualitative Interviews
Damon Scales, MD – damon.scales@sunnybrook.ca
Rob Fowler, MD – rob.fowler@sunnybrook.ca
Vancouver General Hospital, Vancouver
George Isac, MD – George.Isac@vch.ca
University of Alberta Hospital, Edmonton
D. Jim Kutsogiannis, MD – dkj3@ualberta.ca
Hamilton Health Sciences Centre, Hamilton
Maureen Meade, MD - maddock@mcmaster.ca
The Ottawa Hospital, Ottawa – Site for Qualitative Interviews
Lauralyn McIntyre, MD – lmcintyre@ohri.ca
Andrew Seely, MD, PhD – aseely@ohri.ca
Joe Pagliarello, MD - gpagliarello@ottawahospital.on.ca
Royal Columbian Hospital, Vancouver
Steven Reynolds, MD – sreynolds.md@gmail.com
London Health Sciences Centre, London – Expertise in Neurologic Assessments
Teneille Gofton, MD – teneille.gofton@lhsc.on.ca
Mount Sinai Hospital – Site for Qualitative Interviews
Sangeeta Mehta - SMehta@mtsinai.on.ca
Laveena Munshi, MD – laveenamunshi@gmail.com

b. Complementary Study 1 (Prediction Tool for Time to Death after Cardiac Arrest) Collaborators

- Laveena Munshi, MD – Advisor, Critical Care, laveenamunshi@gmail.com
- Alexis Turgeon, MD – Senior Advisor, Neurologic Prognostication - alexis.turgeon@fmed.ulaval.ca

c. Complementary Study 2 (Understanding the experience of DePPaRT families with end-of-life decision-making, and decision-making about organ donation and research participation) Collaborators

- Vanessa Gruben, PhD – Co-lead Investigator - Vanessa.Gruben@uOttawa.ca
- Janet Squires, PhD – Senior Advisor, Qualitative Research, janet.squires@uottawa.ca

d. International Collaborators

Czech Republic
Frantisek Duska, MD, PhD, AFFICM, EDIC
Associated Professor of Anaesthesia and Intensive Care
3rd Faculty of Medicine, Charles University, Prague, Czech Republic
fduska@yahoo.com
Phone: +420 608405551

United Kingdom

Dale Gardiner MBBS, FANZCA, FRCA, BIOETH
Adult Intensive Care Unit, Queen's Medical Centre
Nottingham University Hospitals, Nottingham, United Kingdom
dalegardiner@doctors.org.uk
dalecgardiner@gmail.com

Christian Brailsford
UK Site Coordinator
NHS Blood and Transplant
Bridle Path
Seacroft Leeds LS157TW
Phone: 0113 2155963/ 7525299066(m)
Fax: 0113 8200873
christian.brailsford@nhsbt.nhs.uk

Dan Harvey BMBS, BMedSci, MRCP, FRCA, DICM, FFICM
Consultant Intensive Care Medicine, Research Lead for Critical Care
Nottingham University Hospitals, Nottingham, United Kingdom
danjrharvey@gmail.com

United States

Paul Shore, MD
Dept. of Pediatrics, Section of Critical Care
St. Christopher's Hospital for Children
Drexel University College of Medicine
Paul.ShoreMD@Tenethealth.com

Thomas A. Nakagawa, M.D., FAAP, FCCM
Professor, Anesthesiology and Pediatrics, Wake Forest University School of Medicine
Director, Pediatric Critical Care, Wake Forest Baptist Health, Brenner Children's Hospital
tnakagaw@wakehealth.edu

e. Information Technology Support:

Christophe Herry, PhD (Bioengineering, Ottawa) – cherry@ohri.ca
Nathan Scales, PhD (Bioengineering, Ottawa) - nscales@gmail.com

5. TRAINEES/STUDENTS

a. PhD Students

Alvin Lee (University of Western Ontario)
Loretta Norton (University of Western Ontario)

14.2 APPENDIX B:
PILOT STUDY MANUSCRIPT – Published in CRITICAL CARE MEDICINE JOURNAL

Critical Care Medicine

Vital Signs after Cardiac Arrest Following Withdrawal of Life-Sustaining Therapy: A Multicenter Prospective Observational Study

--Manuscript Draft--

Manuscript Number:	
Full Title:	Vital Signs after Cardiac Arrest Following Withdrawal of Life-Sustaining Therapy: A Multicenter Prospective Observational Study
Article Type:	Clinical Investigation
Keywords:	autoresuscitation, determination of death, donation after cardiac death (DCD), organ donation, vital signs, withdrawal of life-sustaining therapies
Corresponding Author:	Sonny Dhanani, MD Children's Hospital of Eastern Ontario Ottawa, Ontario CANADA
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	Children's Hospital of Eastern Ontario
Corresponding Author's Secondary Institution:	
First Author:	Sonny Dhanani, MD
First Author Secondary Information:	
Order of Authors:	Sonny Dhanani, MD
	Laura Hornby, MSc
	Roxanne Ward, BScN MSc
	Andrew Baker, MD
	Peter Dodek, MD
	Jane Chamber-Evans, BScN MSc
	Rob Fowler, MDCM
	Jan O Friedrich, MD
	Robert M Gow, MD BS
	DJ Kutsogiannis, MD
	Lauralyn Mcintyre, MD
	Franco Momoli, PhD
	Karine Morin, LLM
	Tim Ramsay, PhD
	Damon Scales, MD
	Hilary Writer, MD
	Serafettin Yildirim
	Bryan Young, MD
	Sam Shemie, MD
Order of Authors Secondary Information:	
Manuscript Region of Origin:	CANADA
Abstract:	Objective: Controversies regarding the process and timing of the determination of

	death for controlled organ donation after circulatory death (DCD) persist. This study assessed the feasibility of conducting a prospective, observational, study of continuous monitoring of vital signs for 30 minutes after the clinical determination of death in 5 Canadian intensive care units. Waveform data was analyzed. Design: Prospective observational cohort study. Setting: 1 pediatric and 4 adult Canadian intensive care unit. Patients: 1 month of age or older, admitted to the ICU, and for whom a consensual decision to withdraw life-sustaining therapies had been made, with an anticipation of imminent death. Measurements: Invasive arterial blood pressure, electrocardiogram, and oxygen saturation plethysmography activity were recorded and reviewed for 30 minutes after declaration of death. Feasibility was assessed (recruitment, consent rate, protocol compliance and staff satisfaction). Results: Of 188 subjects screened over 16 months, 41 subjects were enrolled (87% consent rate). Data collection was complete for 30 subjects (73% protocol compliance). In four subjects, arterial blood pressure resumed following cessation of activity. The longest period of cessation of arterial blood pressure before resumption was 89 seconds. The duration of resumed activity ranged from 1 to 172 seconds. No cases of sustained resumption of arterial blood pressure activity were recorded and no instances of clinical autoresuscitation were reported. In nearly all patients (27/30), electrocardiogram activity continued after the disappearance of arterial blood pressure. Conclusions: This is the first observational study to prospectively collect waveform data for 30 minutes after the declaration of death. Further study with a larger sample size may support initial data suggesting that cardiac function does not resume after more than 89 seconds of absence and cardiac electrical activity may not be relevant to declaration of death.
Suggested Reviewers:	Cynthia Gries, MD Assistant Profeesor, University of Pittsburgh griescj@upmc.edu Leader in DCD practice, knowledgable and published in declaration of death for purposes of donation.

14.3 APPENDIX C: SYSTEMATIC REVIEW OF TIME TO DEATH PREDICTORS

In order to inform data collection for the DePPaRT study, a systematic review was performed to determine the risk factors/ risk prediction models/clinical decision tools for patients who undergo withdrawal of life sustaining therapy (including potential DCD candidates) that are associated with and/or predict time to death. A literature search was performed for eligible articles in PUBMED EMBASE and CENTRAL with no language restrictions. Articles were identified in a staged process and were assessed by two investigators independently. The methodological quality of the reporting of the articles was assessed using the Newcastle Ottawa scale. The search revealed 1555 titles that met our search criteria of which 100 abstracts were retrieved for further inspection. In total, 13 full text articles[41-43,57-66] met our pre-specified inclusion criteria, of which six developed/and or validated a prediction tool and five evaluated risk factors associated with time to death after WLST. The following risk factors were found in multiple studies to be significantly associated with time to death after WLST in multivariable analysis: Age, Body mass index, airway type (endotracheal tube versus tracheostomy), mode of mechanical ventilation, ventilator parameters, inotrope and vasopressor use, extracorporeal membrane oxygenation and ventricular assist device use. Several other risk factors were also found to be statistically significant in single studies only. This review showed a number of risk factors to be significantly associated with the time to death after WLST. Based on our findings, below is a table of the variables to be included in the present study:

Potential variables to be collected for time-to-death predictor

Parameter	Type	Detail
Clinical/demographic		
Age	Continuous	
Sex	Binary	
BMI	Continuous	Body mass index
Comorbidities	Categorical	Prior to admission- taken from Chart review
Cardiovascular co-morbidity		
Pulmonary co-morbidity		
Neurological		
Hematological		
malignancy		
Apache II score	Continuous	At ICU admission
Intracranial injury	Categorical	Defined as admission to ICU related to either: Traumatic brain injury, intracranial hemorrhage, cerebrovascular accident, central nervous system infection, and brain tumor.
Reason for admission	Categorical	Admission diagnosis
Vasopressor type and dose	Categorical	Prior to WLST
Cardiac support device	Categorical	Intra aortic balloon pump, Veno arterial ECMO, ventricular assist device
Use of analgesics, type and dose	Categorical	Prior to WLST
Use of sedatives, type and dose	Categorical	Prior to WLST
Clinician's prediction of death	Categorical	Clinicians prediction of death – shorter than or longer than 120 min
Withdrawal style	Categorical	Withdrawal of all treatment modalities at once or in a staggered fashion. Withdrawal of oxygen, withdrawal of respiratory support (decrease in respiratory rate), reduction or discharging of vasopressors/ inotropes, extubation. Tick off one or more.
Accessory airway used after WLST(extubation in this case)	Categorical	Use of oral airway or nasal airway device.
Physiological variables		
Airway type:	Categorical	Airway type prior to WLST define as endotracheal tube, tracheostomy, non invasive mask (used for NIV), natural, nasal or oral airway.
Ventilation mode	Categorical	Ventilation mode to WLST defined as no mechanical ventilation, mandatory or spontaneous
Ventilation type	Categorical	Ventilation type prior to WLST defined as no ventilation, conventional mechanical ventilation, non-invasive ventilation, non conventional mechanical ventilation (ECMO, HFO)

SaO_2	Continuous	Arterial saturation prior to WLST
FiO_2	Continuous	Prior to WLST
PaO2	Continuous	Prior to WLST. Only from an arterial blood gas
PaCo2	Continuous	Prior to WLST-preferably from an arterial blood gas but if not available then venous gas is acceptable-Document time in relation to time of WLST
pH	Continuous	Prior to WLST-preferably from an arterial blood gas but if not available then venous gas is acceptable-Document time in relation to time of WLST
Mean Airway Pressure (MAP)	Continuous	Prior to WLST
Peak inspiratory pressure	Continuous	Prior to WLST
Spontaneous respiratory rate	Continuous	Respiratory rate prior to WLST
Set respiratory rate	Continuous	Respiratory set (for continuous mode)
PEEP	Continuous	Prior to WLST
Heart rate	Continuous	Prior to WLST
Blood pressure	Calculated	Prior to WLST
Neurological variables		
GCS score	Continuous	Prior to WLST. Document total score and its three individual components
corneal reflex	Binary	Prior to WLST defined as present or absent
Cough/ gag reflex	Binary	Prior to WLST defined as present or absent
Extensor or absent motor reflex	Binary	Prior to WLST
Pupillary light reflex	Binary	Prior to WLST defined as present or absent
CT scan	Continuous	Prior to WLST defined as validated score

14.4 APPENDIX D: ELIGIBILITY CRITERIA FOR DCD

The criteria to determine eligibility for DCD are as per the national recommendations produced in 2006[48]. Absolute contraindications to DCD are as per Blackstock et al 2013[50] The following recommendations are taken from this article.

As a general rule, eligibility criteria are similar to those for organ donation after NDD and should be based on demographic, age and organ-function criteria detailed in the previous CCDT forum[49]

Given that the province of Ontario performs the largest number of organ transplants per year in Canada, we will also use the following age and organ specific criteria from Trillium Gift of Life, the Ontario organ procurement organization.

If the potential study subject has any of the following they are considered to NOT eligible for DCD.

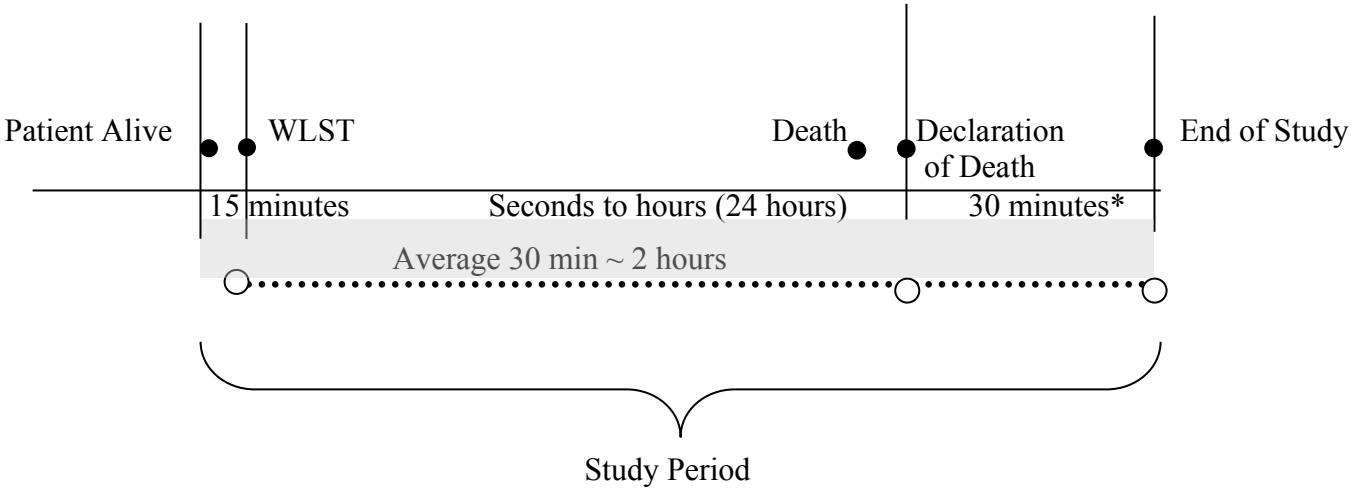
- >79 years of age
- Active or remote melanoma
- Active malignancy
- Metastatic malignancy or high grade brain tumour
- Serious unresolved sepsis or systemic infection
- Intravenous drug abuse
- Human T-cell leukemia-lymphoma virus
- Systemic viral infection (measles, rabies, etc..)
- Prion related disease
- Herpetic meningoencephalitis

Provincial practice warrants further investigation before excluding a potential DCD patient and may still have donation occur under 'extended' DCD criteria. Thus, for our study the following will be included as DCD-eligible:

- Bacteremia alone
- Non-melanoma skin malignancies and some primary non- metastatic brain tumours
- Documented hepatitis B, or C
- Documented HIV

14.5 APPENDIX E:
CONSENT FORMS AND LETTER OF INVITATION TO PARTICIPATE
(See attached document)

14.6 APPENDIX F:
STUDY PERIOD OF DATA COLLECTION



*** Please note that for patients who become DCD donors, the period of time for collection of monitored waveform activity will be up until the removal of organs rather than 30 minutes**

14.7 APPENDIX G: INFORMATION SYSTEMS (IS) REQUIREMENTS

Clinical Requirements:
Pulse oximeter plethysmography, arterial blood pressure and ECG recordings are to be collected from at least 15 minutes prior to the time of WLST until 30 minutes (or up until removal of organs for patients undergoing DCD) post declaration of death. At certain sites with specific expertise, end-tidal capnography, electroencephalogram, and electromyogram waveforms will also be collected for this same time period.

Protocol:
Creation of a customized system for electronic data capture: A customized system for electronic data capture of vital sign waveforms and electronic case report forms (eCRFs) will be created by the team at **The Dynamical Analysis Laboratory (DAL).** DAL is a research lab at the Ottawa Hospital Research Institute (OHRI), affiliated with the Research Institute at the University of Ottawa and the research arm of The Ottawa Hospital. Their work focuses on complexity science, variability analysis and their applications to clinical problems. Under the direction of Dr. Andrew Seely (note, Dr Seely is also the Ottawa hospital site investigator for the DePPaRT study), they have developed Continuous Individualized Multi-organ Variability Analysis (CIMVA) software that provides comprehensive variability calculation and visualization tools. The DAL team of biomedical engineers and computer scientists are expert in harvesting waveforms from the bedside monitors of critically ill patients and making the data available for rapid, digital processing and review. For our study, a Biomedical Engineer will create a standard platform capable of integrating different monitoring systems to a long-term electronic repository. We have budgeted for funds to allow the Biomedical Engineer to travel to the sites to assist with the set-up and integration of this system. Based on our experience with our pilot study, we have found that it will be critical to establish working relationships with each site's information technology support and biomedical personnel to facilitate implementation of such an electronic system. These funds will also allow for on-site training on the use of this web-based electronic data capture system. A web and database design specialist will develop a centralized website for data entry and storage, maintain the web server and data storage. The initial design and setup will be contracted out to a web and database specialist.

Waveform data collection: Waveforms comprise arterial blood pressure data (sampled at125Hz or 300Hz) ECG data (125Hz with beat annotations at 1kHz; or 300Hz) and at specific sites EEG (100Hz) and end-tidal CO_2 capnography (62.5Hz, 125 Hz or 300Hz). Although ICU monitors have CO_2 capnography as an optional module, with the exception of EEG, all the other waveforms are routinely performed and displayed. The data is collected by bedside ICU monitors at each of the study sites (e.g. Phillips Intellivue MP70, Datex Ohmeda S/5 monitor, etc.). The data is automatically or manually saved using commercially available software (e.g. *Data Export* feature on the Phillips central ICU network, *iCollect* on GE Datex Ohmeda S5 iCentral ICU network, Excel Medical Electronics *BedmasterEx*), previously tested by the DAL team and successfully used in

previous clinical studies. Data collection will begin at least 15 minutes prior to the WLST and will continue for up to 30 minutes post declaration of death. The de-identified waveform data files are then uploaded directly to the *https://deppart.org/* website (see below). This system will provide comprehensive beat-to-beat waveform data collection with online, remote reviewing of de-identified patient data that will not interfere with local hospital data collection practice/procedures.

https://deppart.org/: Due to the need to centralize data analysis, the need to work with large data files, and the need for a standardized approach at different centers, the DAL team will create a web-enabled DePPaRT engine. Along with clinical data using secure eCRF's, the waveform data files will be compressed and uploaded to a central secure website (*https://deppart.org/*) for data storage and variability analysis. As done for previous studies by the DAL team, the website will be built with automated data back-up and all uploaded data will be de-identified and password protected[55,56].

Waveform Analysis: After the clinical data and waveform data files are uploaded to https://deppart.org/; variability analysis will be performed by the Continuous Multiorgan Individualized Variability Analysis (CIMVA) software engine. The CIMVA engine performs the following functions: (a) conversion of waveform data files into Matlab data files, (b) Waveform parameters identification (e.g. ECG beats, CO_2 breaths, ABP systolic/diastolic events, etc.) (c) creation of interval time series from waveform parameters, (d) quality assessment of waveform and interval time series and elimination of artifact and (e) Comprehensive continuous variability analysis. Christophe Herry, (Team Leader of the Ottawa Hospital Dynamical Analysis Lab) will be the resource available for managing the CIMVA analysis.

14.8 APPENDIX H:
DATA COLLECTION TOOLS

1. **Case Report Form (see attached document)**

2. **Procedure Forms (**"Prediction of Time to Death Form", "Declaration of Death Checklist Form" and "CT Scan (Head) and Marshall Score Form", see attached documents)

3. **Adjudication of Physiologic Waveform Activity**

Reconsideration of donation after circulatory determination of death (DCD) has progressively occurred. The medical standards for NDD have been established. No such standards exist for the circulatory determination of death. Patient safety and public trust in organ donation rely on clearer parameters of practice.

This prospective, observational, multicentre, will collect recording of the physiological changes of the heart and brain during the dying process, following withdrawal of life sustaining therapy. It will also record the time periods associated with these physiologic changes and report any reversal of activity that may occur.

The study will respond to continued calls for more research in this area by acquiring much needed scientific data to address concerns about DCD, and help establish accepted medical practices.

OBJECTIVE OF ADJUDICATION

1. To review continuous physiologic waveform data sets (Electrocardiogram, Arterial Blood Pressure) from 30 minutes prior to 30 minutes after the clinical declaration of death
2. To independently document the cessation of signal representing electrical or mechanical cardiac activity
3. To document any resumption of signal and subsequent cessation
4. To identify true activity versus artifact

GENERAL COMMENTS

1. Some data sets may be missing one of the 2 measurements. Please attempt to document those that are available and mark NA (not available) when necessary
2. Review 2 measurements individually (ECG and ABP)
3. Time is noted on each strip. Each strip is 6 seconds and each small box(1mm) is 0.2 seconds (note: some strips are labeled at the 5 second interval)
4. Identify times to the nearest second and descriptor for all 3 measurements
5. To note: exact times are not necessary, rough estimates of time points are acceptable
6. Refer to definitions/descriptors (worksheet 2). "Cessation" is defined as absence of signal/activity for 1 minute. "Activity" is further defined as a minimal recognizable pattern that could be considered a signal
7. Refer to appendix A for examples of "Activity", "Artifact", or "Present but Not Identifiable"

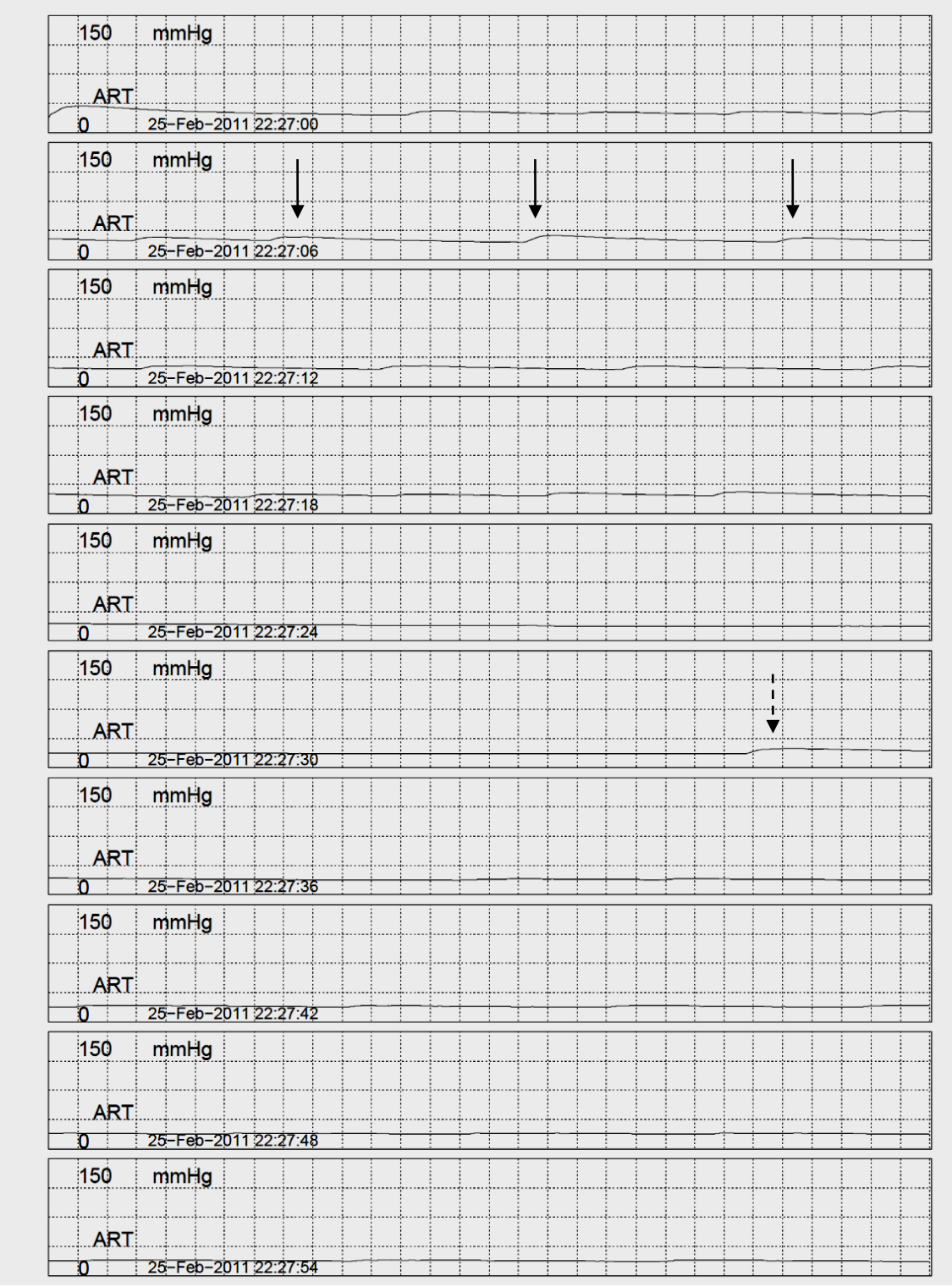
STEP 1 using worksheet 1-ECG (electrical) ACTIVITY

1. Review data strips identified "electrocardiogram" or "ECG"
2. refer to definitions/descriptors (worksheet 2)
3. identify the start time (hh:mm:ss) *and* the associated ABP at that time point
4. identify the time of cessation of activity (hh:mm:ss) *and* the associated ABP activity at that time point
5. identify the time of resumption of activity (hh:mm:ss), if any, otherwise enter "nil"
6. if resumption of activity has occurred, then again identify time cessation of activity (hh:mm:ss)

STEP 2 using worksheet 1-ABP (arterial wave) ACTIVITY

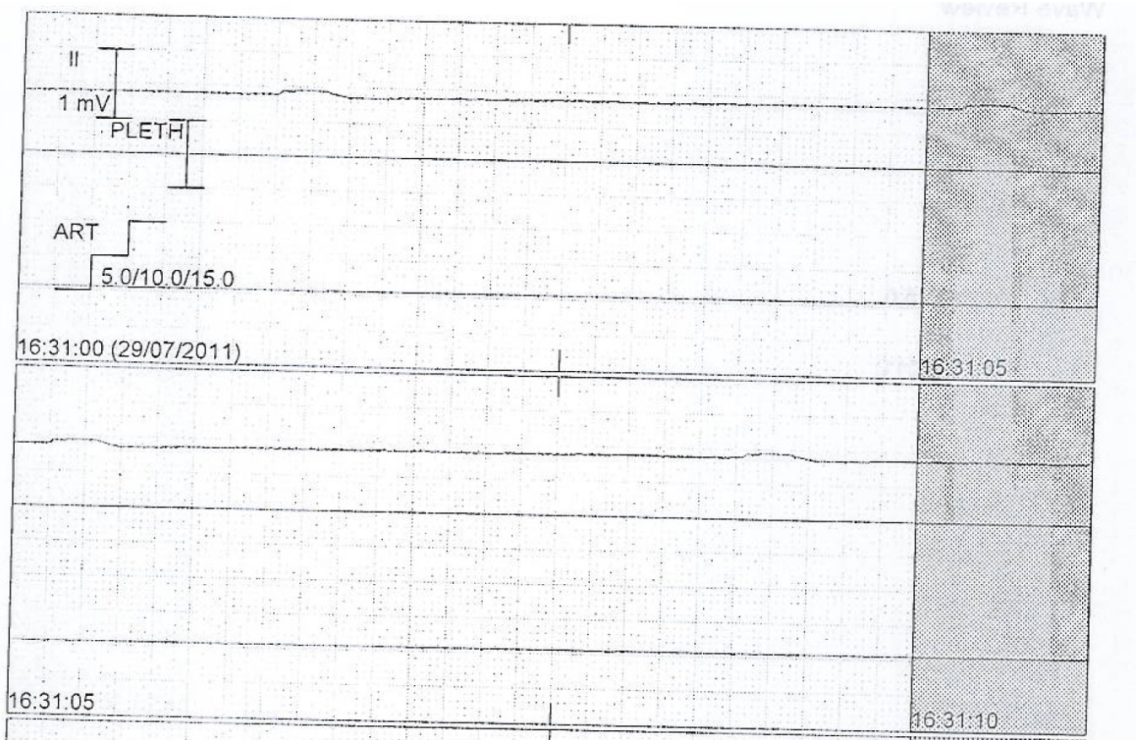
1. Review data strips labeled "ABP" or "Art"
2. refer to definitions/descriptors (worksheet 2)
3. identify the start time (hh:mm:ss) *and* the associated electrical ECG activity at that time point
4. identify the time of cessation of activity (hh:mm:ss) *and* the associated electrical ECG activity at that time point
5. identify the time of resumption of activity (hh:mm:ss), if any, otherwise enter "nil"
6. if resumption of activity has occurred, then again identify time cessation of activity (hh:mm:ss)

EXAMPLE – Activity (Present/Absent)



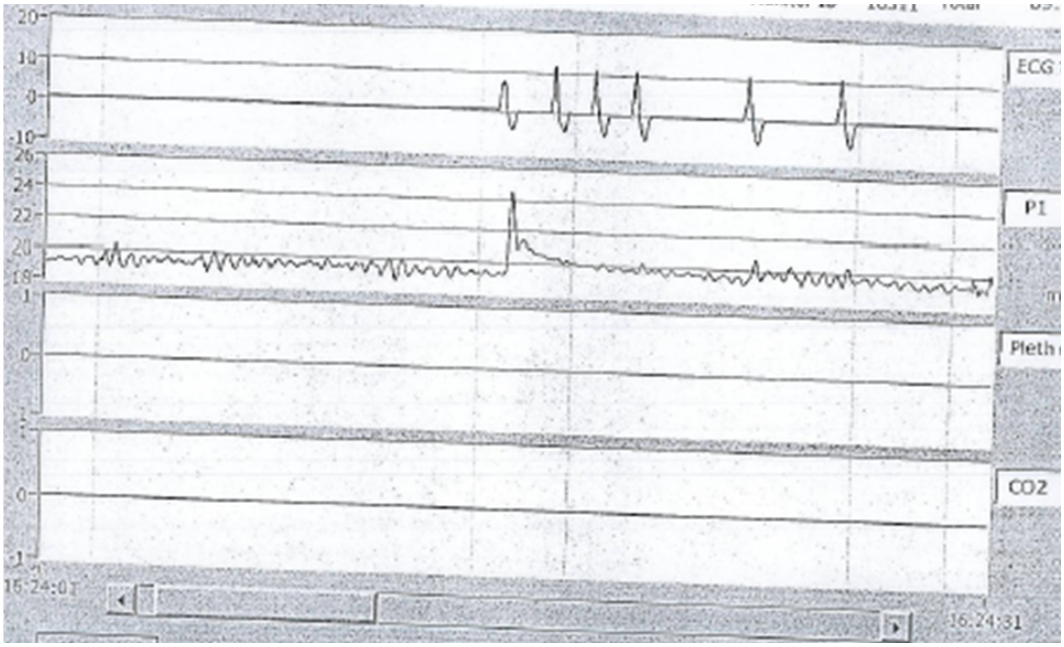
"present (P)" – solid arrows mark signal likely representing pulsatile activity. No interpretation is made on quality or function
"absent (A)" – dashed arrow marks last signal likely representing pulsatile activity or cessation for 60 seconds. One may interpret subtle signal prior to or after marked dashed arrow

EXAMPLE – Present but not Identifiable



"present but not identifiable (PNI)" – solid arrows mark signal present but not clearly identifiable as either atrial or ventricular electrical activity. This may or may not be associated with arterial pulse signal

EXAMPLE – Artifact



"present (P)" – solid arrow marks signal likely representing pulsatile activity. No interpretation is made on quality or function

"artifact (ART)" – dashed arrow marks signal likely representing artifact

Definitions

Waveform	Term	Short form	Description
ECG	present	***P***	atrial and/or ventricular electrical activity present
	present but unknown/not identifiable	***PNI***	signal present but clearly not identifiable as atrial or ventricular activity in origin
	absent	***A***	no atrial or ventricular electrical activity without recurrence for at least 60 seconds
	artifact	***ART***	artifact, in your opinion not representing true activity (see appendix A for example)
ARTERIAL WAVE	present	***P***	first occurrence of contour wave
	present but unknown/not identifiable	***PNI***	signal present but not identifiable as pulsatile activity
	absent	***A***	last contour wave without recurrence for at least 60 seconds
	artifact	***ART***	artifact, in your opinion not representing true activity (see appendix A for example)
	"Cessation"		absence of activity for 1 minute
	"Activity"		a minimal single recognizable pattern that could be considered a signal

ECG Activity	*Time (hh:mm:ss)*	*Associated Arterial Wave*	**Comments**
Start:			
Absent/Cessation (if any)			
Resumption (if any)			
Cessation again (if any)			
Arterial Wave	*Time (hh:mm:ss)*	*Associated ECG*	**Comments**
Start:			
Absent/Cessation:			
Resumption:			
Cessation again (if any)			

14.9 APPENDIX I: LETTERS OF SUPPORT

Canadian Institutes of Health Research
160 Elgin Street, 9th Floor
Address Locator 4809A
Ottawa, ON, K1A 0W9
CANADA

October 15th, 2011

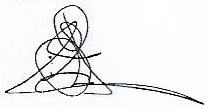
RE: Planning Meeting for the Development of an International Interdisciplinary Research Network to Study the Determinants of Death after Cardiac Arrest

The availability of suitable organs for transplantation remains a significant public health issue. In order to increase the number of available organs and meet the needs of patients and families wishing to donate, many countries have advocated for, and implemented, a process of donation after cardiac death (DCD). Prior to DCD the only means to donate was following the diagnosis of neurological death – brain death.

However, unlike brain death, DCD remains controversial. As outlined in the background of their grant proposal, concerns remain around heterogeneity in definitions of what constitutes an acceptable period of circulatory arrest. Although a consensus conference in Canada has developed standards of care and practice, these definitions are not universally accepted. At the center of the issue is the "dead donor rule". Specifically, the donation of organs cannot cause the demise of the donor. Therefore a definition of death that is reliable, measurable and based upon physiological principles is required.

The importance of developing a consensus on current gaps in knowledge, practices and solutions to close these gaps is urgently needed. In Canada alone, despite the development of DCD guidelines, many jurisdictions have opted not to perform DCD in the face of these knowledge gaps and perceived arbitrariness of definitions. Clearly broader consultation needs to occur. As such the proposal by Dr. Dhanani and collaborators is welcome. He has assembled an international group of experts and stakeholders. The objectives of the meeting are relevant and need to be addressed in a systematic fashion. As such we are very supportive of this application.

Sincerely



John Granton MD FRCPC
President
Canadian Critical Care Society.

Nottingham University Hospitals NHS
NHS Trust

Adult Intensive Care Unit
Queen's Medical Centre Campus
Derby Road
Nottingham
NG7 2UH
Tel: 01159249924 ext. 66241
Email: dale.gardiner@nuh.nhs.uk
dalegardiner@doctors.net.uk

17th September 2012

Dr. Sonny Dhanani
Children's Hospital of Eastern Ontario
Division of Pediatric Intensive Care
401 Smyth Rd
Ottawa Ontario K1M 2B5

Re: CIHR Program Grant in Transplantation Research - Canadian National Transplant Research Program

Dear Dr. Dhanani,

My support of the Canadian led Determination of *Death Practices in the Intensive Care (DDePICt) Research Program*, comes with the full backing of the UK National Organ Donation Committee and UK NHS Blood and Transplant.

I will be very pleased to collaborate as a Site Investigator and as the UK Lead Investigator, for your observational study, of the physiologic changes occurring during withdrawal of life sustaining therapies and in the post mortem period following cardiac arrest. The UK is aware that this study is part of the Canadian National Transplant Research Program and is being submitted to the CIHR Program Grant in Transplantation Research competition. I have read and support this proposal and its rationale.

The results of this innovative and essential study promise a significant contribution to our knowledge relevant to the complex professional, legal and ethical issues surrounding the determination of death for Donation after Cardiocirculatory Death (DCD). This form of organ donation now accounts for 45% of all deceased donation in the UK and it is vital we resolve the outstanding scientific questions this study will address.

I look forward to my work with your team on this exciting and ambitious project.

Yours sincerely,

Dr Dale Gardiner
Intensive Care Consultant
Regional Clinical lead for Organ Donation, Midlands

14.10 APPENDIX J:
BUDGET JUSTIFICATION

Personnel Costs

Project Manager: This project will involve the set up and implementation of this protocol in 13 Canadian ICUs across the country.
This will require a 0.32 full time equivalent (FTE) in Year 1 and Year 2 and 0.2 FTE in Year 3. We estimate an hourly rate of $40/hr plus 23% benefits with a 5% yearly increase.

Year 1: 12 HR/WK x $40/HR x 52 WK + 23% benefits =	$30,701
Year 2: 12 HR/WK x $42/HR x 52 WK + 23% benefits =	$32,236
Year 3: 7.5 HR/WK x $44/HR x 52 WK + 23% benefits =	$21,106
TOTAL:	**$84,043**

Research Coordinator: A Senior Research Coordinator, with experience in multi-centre trials and background in health sciences, will lead the set up and implementation aspects of the study. During the initial study start-up period, the Research Coordinator will be responsible for liaising with site investigators, establishing communications with the Research Assistants, and study personnel at the two sites, and completion of Ethics Committee applications, regulatory document filing, training study personnel, assisting with the final development of the case report form, and study procedures manual. Once the study is established at all sites, the Research Coordinator will be responsible for ongoing communication between all study personnel, including tracking patient enrollment, monitoring of data verification, protocol adherence and ensuring that the study is conducted according to the ICH Guidelines of Good Clinical Practice. The Research Coordinator will produce regular reports for the Project Manager, Principal Investigator, and the Steering Committee as requested. This will require a 1.0 FTE in Year 1 and Year 2 and 0.5 FTE in Year 3. We estimate an hourly rate of $35/hr plus 23% benefits with a 5% yearly increase.

Year 1: 37.5 HR/WK x $35/HR x 52 WK + 23% benefits =	$83,948
Year 2: 37.5 HR/WK x $37/HR x 52 WK + 23% benefits =	$88,744
Year 3: 18.75 HR/WK x $39/HR x 52 WK + 23% benefits =	$46,771
TOTAL:	**$219,463**

Biomedical Engineer, Doctoral level: A Biomedical Engineer (PhD) will be responsible for supervising the monitoring the vital signs data collection at participating sites. This will require a 0.2 FTE in Year 1 and 0.12 FTE in Year 2. We estimate an hourly rate of $32.5/hr plus 26% benefits with a 5% yearly increase.

Year 1: 7.5 HR/WK x $32.5/HR x 52 WK + 26% benefits =	$15,970
Year 2: 4.5 HR/WK x $34/HR x 52 WK + 26% benefits =	$10,025
TOTAL:	**$25,995**

Biomedical Engineer, Masters level: A Biomedical Engineer (MSc) will be responsible for enabling, coordinating and monitoring the vital signs data collection at participating sites. The biomedical engineer will be responsible for the following:

a) Data collection at each participating site

i. Identify interested sites where the data collection is feasible
ii. Assemble and coordinate a site specific data collection project team
iii. Inquire about the site monitoring infrastructure
iv. Consult with monitor vendors and local biomedical/ IT team
v. Design a working solution for collecting data from each participating site
vi. Make sure the data collection solution comply with local ethical and regulatory constraints
vii. Test the data collection procedure at each site
viii. Train the participating site project team on the data collection and storage procedure
ix. Assist all participating sites with technical issues related to the data collection throughout the study

b) Development of Standard Operating Procedures for the Data Collection
c) Development of custom software drivers for collected data from various monitor vendors
d) Development of software for reviewing and annotating the waveform data. A graphical user interface to rapidly view the waveforms, in association with clinical events, will be built specifically for the DePPaRT study, enabling the following:
    i. Rapid review of multiple waveforms recorded for the same patient, scanning forwards and backwards in time
    ii. Annotate waveforms with comments
    iii. Identify waveform events and associate them with time stamps
    iv. Perform automated detection of well defined waveform events (e.g. lack of any activity > 5 sec)

This will require a 1.0 FTE in Year 1 and 0.65 FTE in Year 2. We estimate an hourly rate of $28/hr in Year 1 and $29.5/hr in Year 2 plus 26% benefits.

Year 1: 37.5 HR/WK x 28/HR x 52 WK + 26% benefits =	$68,796
Year 2: 24.5 HR/WK x $29.5/HR x 52 WK + 26% benefits =	$47,355
TOTAL:	**$116,151**

Site Research Coordinators: Research Coordinators at each site will assist with the initial start up of the study. Because of the sensitive and controversial nature of this project, we anticipate that there may be additional meetings required with the Research Ethics Board (REB) in order to obtain ethics approval. There will also be a need for the Research Coordinators to conduct information and training sessions with the ICU staff. Because of this we have included a budget of $3000 (86 hrs) plus 23% benefits for start up costs. The Coordinators will be responsible for screening patients, approaching eligible families for consent, and completing Case Report Forms. These individuals will have experience in health care (preferably a Critical Care Nurse) and research. The breakdown for these costs are as follows:

Start up costs: 86 HR x $35/HR + 23% benefits x 13 sites =	$47,970
Patient Screening/Enrolment 2 HR/Pt x 500 Pts +10% loss to follow up @ $35/HR + 23% benefits + 5% increase per year =	$50,334
Per patient cost: 250 + 23% benefits x 500 patients =	$153,750
TOTAL:	**$252,054**

Database Setup: We will require a Data Management Specialist to design and setup the database, and includes consultation with a biostatistician. This individual will have experience in SPSS and setting up databases. We estimate an hourly rate of $35/HR for 60 hours, plus 23% benefits. The breakdown is as follows:

60 HRs @ $35.00/HR + 23% benefits =	$2,583
TOTAL:	**$2,583**

Statistical Analyses: The Senior Biostatistician from the OHRI estimated a priori sample size of the study, verified the principle of the statistical analysis of this trial and will be responsible for overseeing the final analysis. We estimate an hourly rate of $75/HR plus 26% benefits for 5 hrs. However, as this is a CHEO RI funded project, there will not be a charge for the statistical analysis.

The breakdown is as follows:

Year 1: 30 HRs @ $75/HR =	$ N/C
Year 2:100 HRs @ $75/HR =	$ N/C
TOTAL:	**$ N/C**

TOTAL PERSONNEL:	**$701,678**

Professional Services & Supplies

Web/database design specialist: A web and database design specialist will be hired to develop a centralized website for data entry and storage, maintain the web server and data storage. The initial design and setup will be contracted out to a web and database specialist. The services of that specialist will be retained for on-demand consulting for maintaining and supporting the website and database for the remainder of the study.

Website design: $75/HR x 4 WKS x 37.5 HR/WK =	$11,250
Website maintenance = $75/HR x1 HR/WK x 104 WK =	$7,800
TOTAL:	**$19,050**

Translation of consent form: We estimate the following translation costs

0.30 cents/word @ 2500 words =	$750
TOTAL:	**$750**

Courier: We will courier Case Report Forms and other related study documents between the Coordinating Centre and each of the Study Sites. This will allow tracking of documents, especially for the transfer of study data. We have estimated $800/yr for FEDEX courier services, based on experience with previous studies.

Courier Services 3 YRs x $800/YR =	$2,400
TOTAL:	**$2,400**

Printing and Copying: Study study documents and Case Report Forms will need to be printed at the Coordinating Centre. We have estimated a cost of $500 per year for this service.

Printing Costs 3 YRs x $500/YR =	$1,500
TOTAL:	**$1,500**

Office Supplies (Coordinating Centre): All of these supplies (paper, file folders) are required for the administration and maintenance of study files. We estimate the cost of these supplies to be as follows:

Office Supplies and Printing/copying of Study Documents/CRF's	
$800 YR1, $500 YR2, $300 YR3 Yrs x $500/YR =	$1,600
TOTAL:	**$1,600**

Teleconferences: We will have quarterly teleconferences with the Steering Committee over the three years of the study to review the progress. In addition we will have teleconferences with the study team for each of the sites as needed. We estimate $100 per teleconference for this expense. The breakdown is as follows:

15 Teleconferences in Year 1 and 12 in year 2 @ $100/teleconference =	$2,700
TOTAL:	**$2,700**

TOTAL PROFESSIONAL SERVICES AND SUPPLIES:	**$29,500**

Travel

Travel: The Research Coordinator or Project Manager and Principle Investigator will need to travel to each study site to conduct training of the site Research Coordinators for the study, which will include all study procedures, data collection and how to obtain the electronic monitoring data from the bedside monitor. We estimate 1 full day of training at each site. Thus, we have estimated $3,000 per site to cover flight, accommodation and meals for this travel. The Biomedical Engineer will also have to visit each site for training and installation of the system for electronic data capture of vital signs tracings. Thus, we have estimated $1,500 per site to cover flight, accommodation and meals for this travel. We have also budgeted $3,000 to travel to conferences to present our findings. Since there are three sites located in Ottawa, the breakdown is as follows:

Start-up and training visits: 10 sites x $3,000 per site =	$30,000
Installation of EDC system: 10 sites x 1,500 per site =	$15,000
Travel to conferences =	$3,000
TOTAL:	**$48,000**

GRAND TOTAL:	**$779,178**

14.11 APPENDIX K:
COMPLEMENTARY STUDY 2 (For participating sites only)

Understanding the experience of DePPaRT families with end-of-life decision-making, and decision-making about organ donation and research participation

Qualitative study conducted in association with the Death Prediction and Physiology after Removal of Therapy (DePPaRT) Project

Investigators: Jennifer Chandler, Jane Chambers Evans, Vanessa Gruben, Janet Squires, Sonny Dhanani

Introduction

This project is a qualitative study to examine the experiences of surrogate decision-makers ("SDM") (typically family members) of dying patients enrolled in the DePPaRT study ("Death prediction and physiology after removal of therapy"). The study will involve those SDMs who were approached to consent to organ donation after circulatory determined death ("DCD"), and then subsequently to the participation of the patient in end of life research in the DePPaRT study. The multisite DePPaRT study (led by Dr. Sonny Dhanani at CHEO) is described in a separate protocol and has been approved by the CHEO Research Ethics Board as of May 2014. This qualitative study will take place at a subset of DePPaRT sites.

We will assess the SDMs' experiences related to:

(a) deciding for or against DCD
(b) their feelings about the organ donation process and the outcomes achieved (e.g., whether or not donation proceeded successfully); and
(c) participating in the DePPaRT study, including the informed consent process for participation and the effect of participation on the bedside experience (e.g., perception of the quality of end-of-life care received).

Specific Research Questions:

Research Questions:

1. What was the SDMs' experience of DCD?
    a. What was their experience of deciding on the withdrawal of life sustaining therapies (WLST) and then organ donation?
    b. Why did they decide for/against DCD?

c. How do they feel about the organ donation outcome in their case? (For some it will have gone ahead successfully, but for others it will not have gone ahead).

2. What was the SDMs' experience of participating in the DePPaRT study?
    a. What was their experience of the consent process?
    b. Why did the consent to participate?
    c. What was their experience of the study monitoring at the bedside?

Background/Present State of Knowledge/Rationale:

In North America, organ donation has typically followed a declaration of brain death since the articulation of the brain-based criterion of death in the late 1960s[1]. Since then, donation after DCD has been infrequent in North America, but is now increasing[2-4]. In the United States, UNOS (the United Network for Organ Sharing) promulgated rules relating to DCD in 2007, and Canadian consensus guidelines on DCD were published in 2006[5]. Several aspects of DCD continue to attract ethico-legal concern and uncertainty[6-10]. One of these concerns has to do with the length of the waiting period between cardiac arrest following WLST and the removal of organs for transplantation. Concerns have been raised about the possibility of auto-resuscitation (the spontaneous return of cardiocirculatory function) during this time period. The DePPaRT study aims to gather knowledge useful to determining the appropriate waiting period prior to removal of organs in DCD. The families approached to participate in DePPaRT will already have made a decision to withdraw life sustaining therapy, and some will also have decided for or against DCD. Our study focuses on the sub-group who were offered DCD, and aims to gather information about the experience of participating in the DePPaRT process of physiological monitoring after WLST, as well as the experience of DCD.

Background and justification for the research questions relating to the experience of DCD

The factors affecting family decisions about organ donation, and their experiences in the process of informed consent have been explored in some detail[11-19]. However, this literature has tended to address donation decision-making in general (typically donation after neurologically determined death NDD), rather than focusing on the specific case of DCD. However, DCD and NDD are different procedures that may raise different ethical and psychological issues, and knowledge about family experiences and the proper approach to informed consent in the context of NDD may not be directly translatable to DCD[20]. In fact, a recently published official joint statement of the American Thoracic Society, International Society for Heart and Lung Transplantation, Society of Critical Care Medicine, Association of Organ and Procurement Organizations and United Network of Organ Sharing Statement on the ethical and policy considerations in DCD declared that, "[f]urther data should be obtained regarding whether people comprehend the distinction between declaring death on neurological or circulatory criteria and whether their preferences for donation are influenced by the distinct processes required

by these two pathways to donation"[21].

As the expansion in DCD is relatively recent compared to NDD[7], there is to our knowledge little information so far on the experience of families in consenting to DCD in particular and none that reflects the experience of Canadian families. This information is important for both the humane practice of DCD, as well as for the successful expansion of DCD programs (where "successful" refers to an increase in the number of donors that is also ethically appropriate). The nature of the family experience in deciding whether to consent to DCD is important both to the family's psychological well-being as well as in obtaining organs for transplant. Family refusal to consent is known to be a significant factor in the loss of otherwise transplantable organs[22,23].

The experience of consenting to DCD differs from that of NDD in several key ways.

(1) Families must decide about the withdrawal of life sustaining therapies, which will result in the death of their loved one. In the case of NDD, no family decision precipitates the death of their loved one. In the practice of DCD, the consensus is that the WLST decision must be made prior to and separate from the discussion of organ donation. Although this is the case, families may or may not perceive them as separate decisions, and the proximity of the two decisions may mean that they affect each other. Any discomfort with the WLST decision might colour the organ donation decision in DCD, which must be made around the same time[24].

(2) In DCD, discussions about donation necessarily precede death, while in NDD they need not occur before the declaration of death. As a result, issues around the timing of the declaration of death and the organ donation decision are possibly different. The general consensus is that for NDD, declaration of death should precede and be decoupled from the organ donation decision, so that families have some time to accept the death before being asked to consider organ donation[25]. However, recent literature questions whether decoupling does lead to increased donation rates[26]. In DCD, the issue of timing is necessarily different.

(3) It is not clear that donation will go ahead in cases of DCD (as a patient may not pass away within the necessary time window). There are uncertainties also in whether a donation will proceed in the case of NDD, although failed donation is less frequent. Little is known about the reaction of families to a failed donation once they have consented to DCD[27,28].

(4) Mistrust or confusion surrounding the brain death diagnosis (which is known to affect NDD) is not an issue in the case of DCD[29]. On the other hand, ethicists have raised the concern that end of life treatment decisions may be altered by the prospect of organ donation. As a result, mistrust in the DCD context might center on the issue of whether the treatment team has done all possible to save a loved one. This latter source of mistrust may also apply in NDD, particularly where the brain death diagnosis is rejected. Nonetheless, physicians proposing WLST and possibly DCD have made a judgment of medical futility in relation to a living patient, whereas they have determined death for a

possible NDD patient. The types and intensities of public mistrust/understanding may vary between these two contexts. As Gries et al[21] point out, "[f]or the majority of DCD cases in which the patient cannot communicate preferences, families have an integral role because their consent for the withdrawal of life-sustaining therapy is required even if organ donation has been authorized through first-person consent. Further research is needed to better understand the effects of organ donation on family members' bereavement and perceptions of the quality of end-of-life care after decisions to participate or not in the DCD process".

Research Design/Methods/Analysis

Study Design

This will be a qualitative descriptive study of SDM experiences related to DCD and participation in end-of-life research. This type of qualitative study seeks to gather and describe the details of an experience or event in a manner that remains as close as possible to the data rather than in a manner that seeks to read into or beyond the data to construct a theory or other more elaborate interpretative account of the data.[30-32] This approach is particularly well-suited to documenting experiences in minimally explored areas.[33] There is little data about the experience of families who participate in physiological research during the emotionally difficult and important period of WLST. Similarly there is little data specific to the experience of donor families in the DCD context. Although interpretative transformation of the data by researchers is unavoidable, the method of qualitative description seeks to remain close to documenting the subjective experiences of respondents in their own terms. This (qualitative descriptive) approach is commonly used to gather and present information about the experiences of participants in a range of health-care practices,[34-37] including organ donation.[38]

Study Population - Sampling

In qualitative research, there are no hard rules about sample size; while 6-8 participants often suffice for a homogeneous sample, 12-20 are commonly needed when looking for disconfirming evidence or trying to achieve maximum variation.[39] We desire maximum variation. We will use the concept of data saturation, i.e., we will conduct interviews until no new themes emerge. We will use purposive sampling to recruit up to 20 individuals in each of the following three groups:

1. SDM consented to DCD, and DCD was successful.
2. SDM consented to DCD, but DCD was unsuccessful (e.g., time to death was too long, organs were not viable, etc.); and
3. SDM refused DCD.

The purpose of selecting participants from these three groups is to ensure responses that enable us to compare the experiences of SDMs who differ in several key variables of interest in our study (experiences of consenting to and refusing DCD, and the effects on SDMs of the DCD outcome).

Sample Size Justification

Given our sampling method and the use of an in-depth (45-60 minutes) interviews of SDMs, we estimate that a sample size of 12-20 participants for each of the three groups above (total of 36-60) will be sufficient to generate a rich description of the experiences within each group, and to allow us to draw comparisons across groups, in line with the study objectives. We are guided in our estimate of the target sample size by our review of similar previously-published qualitative interview-based studies of family decision-making about organ donation (typically after neurological determination of death).[40-45]

Inclusion and Exclusion Criteria

Since we are interested in SDMs' experiences in relation to the DePPaRT study as well as in relation to DCD decision-making, we will be studying the subset of DePPaRT SDMs who were offered the option of DCD (and consented or refused), and then were offered and consented to participation in DePPaRT.

Inclusion Criteria:

- SDM who has been offered DCD (and consented or refused).
- SDM of an adult decedent(s)
- English or French speaking SDMs.

Exclusion Criteria:

- SDM who were not offered DCD.
- SDM for pediatric decedents.
- Non-English or French-speaking.

Subject Recruitment

Families will be approached to consent to participate in the DePPaRT study only after they have made a decision to withdraw life-sustaining therapy, and have decided for or against DCD. During the course of the informed consent process for the DePPaRT study, those families who have previously made a decision for or against DCD will be asked if they would allow this research team to contact them (starting 4 months after the death) regarding potential participation in this qualitative study. Families will be clearly informed that the consent they give at the time of the DePPaRT is only to receive a preliminary phone call for information and that they will have the right to accept or refuse to participate in the qualitative study at that time. When the potential participant agrees to be contacted for follow-up, they will provide their contact information, which will then be provided to the qualitative study team using the password protected, encrypted, secure study website (www.deppart.org). Only the qualitative study investigator who will be contacting the participant will have access to the participant's contact information. Participants who decline to participate in the study when contacted for follow up at 4

months after the death of their family member will have their contact information destroyed.

For each participant who agrees to follow up contact, the DePPaRT research co-ordinator at each site will note whether the SDM consented to or declined DCD, and whether donation actually took place.

Informed consent process

For those families who have consented to a follow-up phone call, a reminder letter and a blank copy of the information and consent form will be sent to the SDM. The reminder letter will inform them that there will be a telephone follow up about 1 week after its receipt.

A member of the qualitative research team will contact the participant by phone and invite them to be part of a semi-structured interview. This team member will review the process outlined in the information and consent form that the SDM has received. Time to ask questions will be offered. No member of the qualitative research team will have had any prior contact with or role in the care of the patient or families.

If the participant agrees to be interviewed, the research team member will set the date and time for the interview and note that the consent is not confirmed until the form is signed and they have had the opportunity to ask more questions. This will take place at the time of the interview.

Where it is necessary to conduct the interview by telephone (because the participant prefers, or lives too far away from the hospital), the participant will be asked to send the signed consent form to the research team member by mail, email or fax prior to the date of the telephone interview.

If the participant decides not to be part of the qualitative study, the research team member will thank the participant for their involvement. At that time, contact information for the participant will be destroyed and the study team will have no further contact with the participant.

Data Collection: Semi-structured interviews

We will use semi-structured interviews (45-60 minutes in length) to collect data from the participating SDMs. An interview guide for each of the three participant groups is included at APPENDIX A. This approach has three core advantages: (1) it allows participants to respond relatively freely, to illustrate concepts and to present individual perspectives that the interviewer can probe further; (2) a semi-structured interview guide will increase the likelihood that busy participants cover the topics of interest in an efficient manner; (3) such a guide facilitates flexibility, so that an interviewer may explore in greater depth issues that may arise which are not addressed by the guide.[46-47]

The interviews will be conducted by telephone or in person, depending upon the preferences and circumstances of the participant, at a time that is convenient for the participant. If a participant wishes to participate in the study but not by telephone, an in-person interview will be conducted in a private space (in their home or a room within the university or hospital). All interviews will be audio-recorded to ensure the accuracy of transcription and data analysis.

The interview questions will address the following topics for all three groups of participants:

- their experience during the informed consent process, including their experience of making a decision about WLST, then DCD, and then the DePPaRT monitoring study,
- whether the DePPaRT monitoring study affected their experience with their loved one at the end of life.

In addition to these, the three groups will be asked questions that vary according to their decision regarding DCD:

Group one participants will be DePPaRT study participants who consented to DCD, which proceeded successfully.

- their experience of the DCD process
- their feelings about the completed donation.

Group two participants are similar to group one participants with the exception that the donation was unsuccessful.

- their experience of the DCD process (those aspects that did occur, even though donation did not ultimately occur)
- their feelings about the fact that donation did not proceed.

Group three participants will be DePPaRT study participants who refused DCD. The focus of the questioning will be to understand:

- the decision to refuse donation, and their feelings about that refusal.

All participants will be offered an information sheet describing further support that is available in the same community as the relevant hospital if required (social services, pastoral care, grief support programs). This information will be offered over the telephone for those participants who have opted for an interview by telephone.

Data Analysis

To monitor the progress of the interviews, permit follow-up of issues that may emerge from the data, and allow us to assess whether we have reached saturation, interviewing, transcription, and analysis will proceed concurrently. The digital recordings will be

transcribed verbatim and verified by the interviewer prior to analysis. Data will be imported into qualitative data analysis software to facilitate analysis.

Team members will review the transcripts inductively, using content analysis.[30,33] The approach is "a research method for the subjective interpretation of the content of text data through the systematic classification process of coding and identifying themes or patterns".[33,48] Our analysis will be conducted in three phases. Phase 1 will be guided by principles of *constant comparative analysis.*[49-50] The data will be constantly revisited after initial coding comparing it to all other pieces of data that are either similar or different, until it is clear that no new codes are emerging.[49-50] This will occur in two steps: coding and categorizing. Team members will code the data using the following process. Several transcripts will be coded by the whole team, which will meet as a group to discuss the key ideas in the transcripts and to define the emerging codes. Codes will be operationally defined in order to be consistently applied throughout the data. Codes will then be placed into broad categories, which will become our major units of analysis. Comparisons between multiple categories will be carried out in order to locate similarities and differences between them. Pairs of team members will code the transcripts, with the whole team maintaining contact to compare their interpretations regularly. Differences between the coders will be discussed and consensus sought.

In Phase 2, the study team will meet to combine the coded categories into over-arching themes that accurately depict the data. In Phase 3, the team will examine the themes to create a description of the experiences of SDMs, as well as a comparison of the experiences among the three groups in our study.

Throughout the analytical process, we will also write memos to record the analytic process, which will be analyzed in the same inductive fashion outlined above.

Risks/Ethical considerations

The informed consent process for the qualitative study will begin at the time of the DePPaRT study but will require a sensitive and careful approach to ensure that participants are given the opportunity to reflect on the study, its purpose and how it will be conducted.

They will be clearly informed that their participation is voluntary. Because each participant is being approached four to six months following the death of a loved one the process will involve three steps. First, at the time of consent to participation in the DePPaRT study participants will be asked if the qualitative research team may contact them by mail and phone no earlier than 4 months after the death, and their willingness or refusal of follow-up contact will be recorded by the DePPaRT research coordinator. Second, if the participant agrees to follow-up contact, a letter of invitation will be sent along with a copy of the consent form, and will be followed by a phone call one week after estimated receipt of the letter. It is felt that the letter of invitation will be a way of introducing the study again in a non-threatening way to assist the participants to be ready for a phone call from the research team. The consent form will be reviewed during the

follow-up phone call. Participants who agree to be interviewed by telephone will be asked to forward the signed consent form to the research team member by mail, email or fax prior to the date of the telephone interview. For those who have consented to an in-person interview, the interviewer will review the consent form and obtain their signed consent at the time of the interview. We are aiming to initiate contact and carry out interviews in the 4-6 months window after death, although scheduling may require some interviews to take place later than that (but never earlier).

Because of the sensitive nature of the topics some participants may find the discussions difficult. Participants will be offered an information sheet describing further support that is available in the same community as the relevant hospital if required (social services, pastoral care, grief support programs). Where interviews are conducted by telephone, this information will be offered over the phone.

Each interview transcript and audio recording will be labeled with a unique identifier and a password protected electronic master list will be created with the names and unique identifiers matched. This master list will be kept separate from the interview files on a secure server at the University of Ottawa. The interviews will be identified only by the unique identifier and stored in a password-protected file on the University of Ottawa server. Only members of the research team will have access to the interview material during the analysis process.

Once the study is complete all interview files and research documentation will be retained for 10 years and will then be destroyed in accordance with REB-accepted procedures.

Budget

Research Assistant

We will recruit a bilingual (French, English) research assistant to work with the team. This person will help to organize and conduct interviews, and will participate in the analysis of transcripts and the preparation of publications.
Year 1: Hourly rate $30 x 10 hours per week x 50 weeks = $15,000
Year 2: Hourly rate $30 x 10 hours per week x 50 weeks = $15,000

Transcription

The one-hour interviews will be transcribed. Depending on the number of interviews required to reach saturation, we may have 36-60 hours. We estimate that each hour of interview time will take 4 hours to transcribe at a cost of $28hour.
Transcription 60 hours x 4 x $28 $6,720

Travel

We will be recruiting participants in four of the DePPaRT sites (the Ottawa Hospital, Sunnybrook Hospital (Toronto), St. Michael's Hospital (Toronto) and London Health

Sciences Center (London). Research team members are currently based in Ottawa and Montreal. We may need to make several trips to Toronto and London to interview participants recruited in Toronto and London, as well as between Ottawa and Montreal.

Toronto and London: 4 trips @ $800	$3,200
Montreal/Ottawa: 4 trips @400	$1,600

Incidental expenses

We will offer $15 to cover parking or travel expenses to participants where interviews take place away from their homes. We also budget an additional $5 per participant to cover refreshments. Assuming half of maximum number of interviews take place in person away from the participants' homes – we budget to cover incidentals for 30 interviews.

Incidentals 30 x $20	$ 600.
TOTAL:	**$42,120**

APPENDIX A – INTERVIEW QUESTIONS

Interview questions and some sub-questions to prompt the collection of data. The interview questions are designed to elicit information relevant to the following research questions:

1. What was the SDMs' experience of consenting to DCD?
    a. What was their experience of deciding on WLST and organ donation?
    b. Why did they decide for/against DCD?
    c. How do they feel about the organ donation outcome in their case? (For some it will have gone ahead successfully, but for others it will not have gone ahead).
2. What was the SDMs' experience of participating in the DePPart study?
    a. What was their experience of the consent process?
    b. What was their experience of the study monitoring?

Interview question 1a

Preamble: You were asked to make some decisions at a very difficult time [6] months ago, having to do with the end of life care of your _____. Families in your position are asked to make decisions about whether to stop treatments (such as removing a breathing machine). If they agree, then some are also asked whether they would like to consent to organ donation on behalf of their loved one. We are trying to understand the factors that guide family decision-making and the things that make this experience easier or harder for families. We would like to ask you a few questions about these decisions in your experience.

We would like to ask you a series of questions about the decisions to stop treatment.

> Can you remember what the discussions were like?
> Who was with you?
> Who spoke to you?
> Did you receive all the information you wanted?
> How did you make these decisions?
> How did you feel about the discussion at the time? Do you still feel the same way now?

Once you made the decision to stop treatment, you were then asked whether you were interested in organ donation.

> Who raised the possibility of organ donation?
> Who spoke to you about organ donation?
> Had you thought about organ donation before it was raised with you? When did the possibility occur to you?
> How did you feel about the discussions surrounding DCD?

Did you feel you received the information you wanted about DCD?
You had to make two big decisions in a short time about stopping treatment and then later about organ donation. Can you tell us about this experience?
Do you think the possibility of organ donation might make the end of life decisions easier or harder for families? Did it have any impact for you at the time?

Interview question 1b

Preamble: People have different reasons for consenting or refusing organ donation for themselves and for their loved ones. We are wondering about how you reached your decision.

Why did you decide for/against DCD?

Interview question 1c (for those who consented to DCD)

[Where donation did ultimately proceed]

Preamble: We know that in your case, your loved one was ultimately able to donate.

How did you learn that the donation was successful?
What did the successful donation mean to you and your family at that time?
Do you feel any differently now that time has passed?
Given what you have been through and knowing what you know now, do you think you would make the same decisions?
Some families consent to donation, but unfortunately the donation cannot proceed in the end. How do you think your experience would have been different if your loved one had ultimately not been able to donate?

[Where donation did not ultimately proceed]

Preamble: We know that in your case, your loved one was unfortunately unable to donate.

How did you learn that the donation could not go ahead?
What did it mean to you and your family at that time to learn that the donation could not go ahead?
Do you feel any differently now that time has passed?
Given what you have been through and knowing what you know now, do you think you would make the same decisions?
Do you think your experience would have been different if your loved one had ultimately been able to donate?

Interview question 2a

What was the experience of the surrogate decision-maker of the informed consent process for research at the time of the death of a loved one?

Preamble

About [6] months ago you were involved in a research study at the time of the death of _____(your husband, wife, son etc). We would like to ask you a few questions about the study and the involvement of you and your family.

First we want to ask you about the consent process:

Who spoke to you about the study in the first place?
P: Sometimes it is the nurse who first mentions, or perhaps the MD. They may have told you and then someone else spoke to you.
What do you remember about the study?
Were you given a chance to ask some questions?
Were you given a copy of the consent form?
The study was done on a very difficult day – why did you say yes to being a part of this study?
Was anyone involved with you in making the decision?
As you think back on the study was there anything else you wished that you had known beforehand?
Would you have any advice for our team if we were to talk to other families about this study?

Interview question 2b

Did the monitoring procedures involved in the study alter the experience of the surrogate at the bedside?

Remember back to the time of the study. We were recording things like heart beats and blood pressure in the 30 minute period following the declaration of death.
Were you aware of the monitoring that was going on?
How did you feel knowing the study was taking place?
Did any part of the study interfere in any way with your ability to be with your family member at the time of their death?
Did your experience match with what you had understood was going to happen during the study?
Would you have any advice for our team if we were doing more research at such a sensitive time?

Interview question 3

Preamble: We are looking for ways to help families in the future who will face the same kinds of decisions that you faced.

Thinking back on the whole experience, what advice would you give to medical and hospital personnel about how to help families?

What advice would you give other families, if you were able to speak to them?

Is there anything else that you would like to share with us about your experience.

References from Complimentary Study 2 Protocol

1. Steinbrook R. Organ donation after cardiac death. The New England journal of medicine 2007;357:209-13.
2. Abt PL, Fisher CA, Singhal AK. Donation after cardiac death in the US: history and use. Journal of the American College of Surgeons 2006;203:208-25.
3. Leichtman AB, Cohen D, Keith D, et al. Kidney and pancreas transplantation in the United States, 1997-2006: the HRSA Breakthrough Collaboratives and the 58 DSA Challenge. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons 2008;8:946-57.
4. Hernadez-Alejandro R, Wall W, Jevnikar A, 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;58:599-605.
5. Shemie SD, Baker AJ, Knoll G, 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;175:S1.
6. Bastami S, Matthes O, Krones T, Biller-Andorno N. Systematic review of attitudes toward donation after cardiac death among healthcare providers and the general public. Critical care medicine 2013;41:897-905.
7. Manara AR, Murphy PG, Ocallaghan G. Donation after circulatory death. British journal of anaesthesia 2012;108:i108-i21.
8. Harrison CH, Laussen PC. Controversy and consensus on pediatric donation after cardiac death: ethical issues and institutional process. Transplantation proceedings 2008;40:1044-7.
9. Doig CJ. Is the Canadian health care system ready for donation after cardiac death? A note of caution. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne 2006;175:905.
10. DuBois JM, Anderson EE. Attitudes toward death criteria and organ donation among healthcare personnel and the general public. Progress in transplantation (Aliso Viejo, Calif) 2006;16:65-73.
11. de Groot J, Vernooij-Dassen M, Hoedemaekers C, Hoitsma A, Smeets W, van Leeuwen E. Decision making by relatives about brain death organ donation: an integrative review. Transplantation 2012;93:1196-211.
12. Walker W, Broderick A, Sque M. Factors Influencing Bereaved Families' Decisions About Organ Donation: An Integrative Literature Review. Western journal of nursing research 2013.
13. Manzari ZS, Mohammadi E, Heydari A, Aghamohammadian, Modabber, Khaleghi E. Exploring families' experiences of an organ donation request after brain death. Nursing Ethics 2012;19:654-65.
14. Vincent A, Logan L. Consent for organ donation. British journal of anaesthesia 2012;108:i80-i7.
15. Sque M, Long T, Payne S, Allardyce D. Why relatives do not donate organs for transplants: 'Sacrifice' or 'gift of life'? Journal of Advanced Nursing 2008;61:134-44.

16. Sque M, Galasinski D. Keeping Her Whole: Bereaved families accounts of declining a request for organ donation. Cambridge Quarterly of Healthcare Ethics 2013;22:55-63.
17. Sotillo E, Montoya E, Martinez V, et al. Identification of variables that influence brain-dead donors' family groups regarding refusal. Transplantation proceedings 2009;41:3466-70.
18. Smudla A, Mihaly S, Hegedus K, Fazakas J. The mistake of communication with relatives of heart-beating donors: Video model. Transplant International 2011;24:246.
19. Singh P, Kumar A, Sharma RK. Factors influencing refusal by relatives of brain-dead patients to give consent for organ donation: experience at a transplant centre. Journal of the Indian Medical Association 2004;102:630, 2, 43.
20. Kalkbrenner KJ, Hardart GE. Consent for donation after cardiac death: A survey of organ procurement organizations. Journal of intensive care medicine 2012;27:253-63.
21. Gries CJ, White DB, Truog RD, et al. An official american thoracic society/international society for heart and lung transplantation/society of critical care medicine/association of organ and procurement organizations/united network of organ sharing statement: ethical and policy considerations in organ donation after circulatory determination of death. American journal of respiratory and critical care medicine 2013;188:103-9.
22. Thybo KH, Eskesen V. The most important reason for lack of organ donation is family refusal. Danish Medical Journal 2013;60.
23. Branco BC, Inaba K, Lam L, et al. Donor conversion and procurement failure: the fate of our potential organ donors. World journal of surgery 2011;35:440-5.
24. Wind J, Snoeijs MG, Brugman CA, et al. Prediction of time of death after withdrawal of life-sustaining treatment in potential donors after cardiac death*. Critical care medicine 2012;40:766-9.
25. Simpkin AL, Robertson LC, Barber VS, Young JD. Modifiable factors influencing relatives' decision to offer organ donation: systematic review. BMJ (Clinical research ed) 2009;338:b991.
26. Siminoff LA, Agyemang AA, Traino HM. Consent to organ donation: a review. Progress in Transplantation 2013;23:99-104.
27. Portmann J. Organ donation and the anguish of failure. Journal of Clinical Ethics 1999;10:324-8.
28. Bellali T, Papazoglou I, Papadatou D. Empirically based recommendations to support parents facing the dilemma of paediatric cadaver organ donation. Intensive and Critical Care Nursing 2007;23:216-25.
29. Sque M, Long T, Payne S. Organ donation: key factors influencing families' decision-making. Transplantation proceedings 2005;37:543-6.
30. Sandelowski M. 2000. Whatever happened to qualitative description? Research in Nursing & Health 23:334-340.
31. Sandelowski, M. 2010. What's in a name? Qualitative description revisited. Research in Nursing & Health, 33:77-84.
32. Neergaard, M.E. et al. 2009. Qualitative description – the poor cousin of health research? BMC Medical Research Methodology. 9:52.
33. Hsieh, H-F and Shannon, S.E. 2005. Three approaches to qualitative content analysis. Qualitative Health Research 15:1277-1288.

34. White, H.E. et al. 2012. "Worse than HIV" or "not as serious as other diseases"? Conceptualization of cervical cancer among newly screened women in Zambia. Social Science & Medicine 74:1486-1493.
35. Murphey, C. 2013. Oral health experiences of pregnant and parenting adolescent women: A qualitative descriptive study. Intl. J of Nursing Studies 50:768-775.
36. Calvin, A.O. et al. 2009. The cardiovascular intensive care unit nurse's experience with end-of-life care: A qualitative descriptive study. Intensive and Critical Care Nursing 25:214-220.
37. Rennick J.E. et al. 2011. Mothers' experiences of a Touch and Talk nursing intervention to optimize pain management in the PICU: A qualitative descriptive study. Intensive and Critical Care Nursing 271:151-157.
38. Sherry, W. et al. 2013. An exploration of knowledge, attitudes and beliefs toward organ and tissue donation among the adult Haitian population living in the Greater Montreal Area. Dynamics 24.1.
39. Crabtree, B., Miller, W. *Doing Qualitative Research*, 4th ed. Newbury Park: Sage; 1992.
40. Bellali, T., Papadatou D**.** Parental grief following the brain death of a child: Does consent or refusal to organ donation affect their grief? Death Studies. 2006;30(10):883-917.
41. Bellali T, Papadatou D**.** The decision-making process of parents regarding organ donation of their brain dead child: A Greek study. Social Science and Medicine. 2007;64(2):439-50.
42. Tong, Y-F. et al. Needs and experiences of Hong Kong Chinese Cadaveric Organ Donor Families. Hong Kong J. Nephrol. 2006;8(1):24-32.
43. Kesselring A, Kainz M, Kiss A**.** Traumatic memories of relatives regarding brain death, request for organ donation and interactions with professionals in the ICU. American Journal of Transplantation. 2007;7(1):211-7.
44. Haddow G**.** Donor and nondonor families' accounts of communication and relations with healthcare professionals. Progress in Transplantation. 2004;14(1):41-8.
45. Moraes EL, Massarollo MCK**.** Family refusal to donate organs and tissue for transplantation. Revista Latino-Americana de Enfermagem (RLAE). 2008;16(3):458-64.
46. Morse, J., Field, P. *Qualitative research methods for health professionals*, 2nd ed. Thousand Oaks, CA: Sage, 1995.
47. Marshall, C., Rossman, G. *Designing Qualitative Research*, 5th ed. Newbury Park: Sage, 1989.
48. Elo, S. and Kyngas, H. The qualitative content analysis process. Advanced Nursing 2008;62(1):107-115.
49. Hewitt-Taylor, J. Use of constant comparative analysis in qualitative research. *Nursing Standard* 2001;15:39-42.
50. Glaser B, Strauss A: *The discovery of grounded theory.* Hawthorne, NY: Aldine; 1967.

REFERENCES

References from full DePPaRT Protocol

1. The Madrid resolution on organ donation and transplantation: national responsibility in meeting the needs of patients, guided by the WHO principles. Transplantation 2011;91 Suppl 11:S29-31.
2. CORR Annual Report. 2011. (Accessed December, 2012, at http://www.cihi.ca).)
3. CORR website October 4, 2012, at (http://www.cihi.ca).)
4. Shemie SD, Hornby L, Chandler J, Nickerson P, Burkell J. Lifetime probabilities of needing an organ transplant versus donating an organ after death. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons 2011;11:2085-92.
5. Organ Donation and Transplantation Activity Report 2012/13. 2014. (Accessed January 23, 2014, at http://www.organdonation.nhs.uk/statistics/transplant_activity_report/)
6. International Figures on Donation and Transplantation - 2011 Newsletter Transplant. 2012. (Accessed January 23, 2014, at http://www.transplant-observatory.org/Documents/NEWSLETTER2012.pdf.)
7. Dhanani S, Hornby L, Ward R, et al. Vital Signs After Cardiac Arrest Following Withdrawal of Life-Sustaining Therapy: A Multicenter Prospective Observational Study. Critical care medicine 2014.
8. Dhanani S, Hornby L, Ward R, Shemie S. Variability in the determination of death after cardiac arrest: a review of guidelines and statements. Journal of intensive care medicine 2012;27:238-52.
9. Wijdicks EF, Diringer MN. Electrocardiographic activity after terminal cardiac arrest in neurocatastrophes. Neurology 2004;62:673-4.
10. Dhanani S, Ward R, Hornby L, Barrowman NJ, Hornby K, Shemie SD. Survey of determination of death after cardiac arrest by intensive care physicians. Critical care medicine 2012;40:1449-55.
11. Hernadez-Alejandro R, Wall W, Jevnikar A, 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;58:599-605.
12. Moser M, Sharpe M, Weernink C, et al. Five-year experience with donation after cardiac death kidney transplantation in a Canadian transplant program: Factors affecting outcomes. Canadian Urological Association journal = Journal de l'Association des urologues du Canada 2012;6:448-52.
13. Halpern SD, Barnes B, Hasz RD, Abt PL. Estimated supply of organ donors after circulatory determination of death: a population-based cohort study. JAMA : the journal of the American Medical Association 2010;304:2592-4.
14. Ausania F, White SA, Pocock P, Manas DM. Kidney damage during organ recovery in donation after circulatory death donors: data from UK National Transplant Database. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons 2012;12:932-6.
15. Abt PL, Fisher CA, Singhal AK. Donation after cardiac death in the US: history and use. Journal of the American College of Surgeons 2006;203:208-25.

16. Leichtman AB, Cohen D, Keith D, et al. Kidney and pancreas transplantation in the United States, 1997-2006: the HRSA Breakthrough Collaboratives and the 58 DSA Challenge. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons 2008;8:946-57.
17. Bastami S, Matthes O, Krones T, Biller-Andorno N. Systematic review of attitudes toward donation after cardiac death among healthcare providers and the general public. Critical care medicine 2013;41:897-905.
18. Doig CJ. Is the Canadian health care system ready for donation after cardiac death? A note of caution. CMAJ 2006;175:905.
19. Bradley JA, Pettigrew GJ, Watson CJ. Time to death after withdrawal of treatment in donation after circulatory death (DCD) donors. Current opinion in organ transplantation 2013.
20. Downie J, Kutcher M, Rajotte C, Shea A. Eligibility for organ donation: a medico-legal perspective on defining and determining death. Canadian journal of anaesthesia = Journal canadien d'anesthesie 2009;56:851-63.
21. Joffe AR, Anton NR, deCaen AR. Survey of pediatricians' opinions on donation after cardiac death: are the donors dead? Pediatrics 2008;122:e967-74.
22. Harrison CH, Laussen PC. Controversy and consensus on pediatric donation after cardiac death: ethical issues and institutional process. Transplantation proceedings 2008;40:1044-7.
23. Wind J, van Mook W, Willems MEC, van Heurn LWE. Higher organ donation consent rates by relatives of potential uncontrolled donors versus potential controlled donors after death. Nephrology Dialysis Transplantation 2012;27:4219-23.
24. Youngner SJ, Arnold RM. Ethical, psychosocial, and public policy implications of procuring organs from non-heart-beating cadaver donors. JAMA : the journal of the American Medical Association 1993;269:2769-74.
25. Kootstra G, Daemen JH, Oomen AP. Categories of non-heart-beating donors. Transplantation proceedings 1995;27:2893-4.
26. Hornby K, Hornby L, Shemie SD. A systematic review of autoresuscitation after cardiac arrest. Critical care medicine 2010;38:1246-53.
27. Gerard D, Vaux J, Boche T, Chollet-Xemard C, Marty J. Lazarus phenomenon: knowledge, attitude and practice. Resuscitation 2013.
28. Greer R, Soar J. Lazarus Phenomenon: confirmation of death after unsuccessful cardiopulmonary resuscitation. Resuscitation 2013.
29. Diagnosis of death after cessation of cardiopulmonary resuscitation, Signal, Reference number 1329. 2012. (Accessed 18 August 2013, at http://www.nrls.npsa.nhs.uk/resources)
30. Nakagawa TA, Rigby MR, Bratton S, et al. A call for full public disclosure for donation after circulatory determination of death in children. Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies 2011;12:375-7; author reply 7-8.
31. Sarnaik AA, Clark JA, Meert KL, Sarnaik AP. Views of pediatric intensive care physicians on the ethics of organ donation after cardiac death. Critical care medicine 2013;41:1733-44.
32. Clute HL, Levy WJ. Electroencephalographic changes during brief cardiac arrest in humans. Anesthesiology 1990;73:821-5.

33. Losasso TJ, Muzzi DA, Meyer FB, Sharbrough FW. Electroencephalographic monitoring of cerebral function during asystole and successful cardiopulmonary resuscitation. Anesthesia and analgesia 1992;75:1021-4.
34. Moss J, Rockoff M. EEG monitoring during cardiac arrest and resuscitation. JAMA : the journal of the American Medical Association 1980;244:2750-1.
35. Kovach AG, Sandor P. Cerebral blood flow and brain function during hypotension and shock. Annual review of physiology 1976;38:571-96.
36. Chawla LS, Akst S, Junker C, Jacobs B, Seneff MG. Surges of electroencephalogram activity at the time of death: a case series. Journal of palliative medicine 2009;12:1095-100.
37. Auyong DB, Klein SM, Gan TJ, Roche AM, Olson D, Habib AS. Processed electroencephalogram during donation after cardiac death. Anesthesia and analgesia 2010;110:1428-32.
38. Borjigin J, Lee U, Liu T, et al. Surge of neurophysiological coherence and connectivity in the dying brain. Proceedings of the National Academy of Sciences of the United States of America 2013;110:14432-7.
39. Reich DJ, Mulligan DC, Abt PL, 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;9:2004-11.
40. Wiegand D. In their own time: the family experience during the process of withdrawal of life-sustaining therapy. Journal of palliative medicine 2008;11:1115-21.
41. Lewis J, Peltier J, Nelson H, et al. Development of the University of Wisconsin donation After Cardiac Death Evaluation Tool. Progress in transplantation (Aliso Viejo, Calif) 2003;13:265-73.
42. Brieva J, Coleman N, Lacey J, Harrigan P, Lewin TJ, Carter GL. Prediction of Death in Less Than 60 Minutes Following Withdrawal of Cardiorespiratory Support in ICUs. Critical care medicine 2013.
43. Shore PM, Huang R, Roy L, et al. Development of a bedside tool to predict time to death after withdrawal of life-sustaining therapies in infants and children. Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies 2012;13:415-22.
44. Thybo KH, Eskesen V. The most important reason for lack of organ donation is family refusal. Danish Medical Journal 2013;60.
45. Branco BC, Inaba K, Lam L, et al. Donor conversion and procurement failure: the fate of our potential organ donors. World journal of surgery 2011;35:440-5.
46. UK Donation Ethics Committee Annual Report. 2011-2012. (Accessed January 27, 2014, at http://www.aomrc.org.uk/publications/reports-a-guidance.html.)
47. Organ Donation after Circulatory Death: Report of a Consensus Meeting. 2010. (Accessed January 27, 2014, at http://www.bts.org.uk/Documents/Guidelines/Active/DCD for BTS and ICS FINAL.pdf.)
48. Shemie SD, Baker AJ, Knoll G, 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;175:S1.

49. Shemie SD, Ross H, Pagliarello J, 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;174:S13-32.
50. Blackstock MJ, Ray DC. Organ donation after circulatory death: an update. European journal of emergency medicine : official journal of the European Society for Emergency Medicine 2013.
51. DeVita MA, Snyder JV, Arnold RM, Siminoff LA. Observations of withdrawal of life-sustaining treatment from patients who became non-heart-beating organ donors. Critical care medicine 2000;28:1709-12.
52. Sheth KN, Nutter T, Stein DM, Scalea TM, Bernat JL. Autoresuscitation after asystole in patients being considered for organ donation. Critical care medicine 2012;40:158-61.
53. Hanley JA, Lippman-Hand A. If nothing goes wrong, is everything all right? Interpreting zero numerators. JAMA : the journal of the American Medical Association 1983;249:1743-5.
54. Steyerberg EW. Clinical prediction models: a practical approach to development, validation, and updating: Springer; 2009.
55. Arnold RC. Assessing continuous heart rate variability in the resuscitation of severe sepsis. Journal of critical care 2010;25:e10.
56. Seely AJE, Bravi, A, Herry, C, Green, G, Longtin, A et al., . Do heart and respiratory rate variability improve prediction of extubation outcomes in a general ICU population? submitted to Critical Care, Sept 2013.
57. Coleman NL, Brieva JL, Crowfoot E. Prediction of death after withdrawal of life-sustaining treatments. Critical care and resuscitation : journal of the Australasian Academy of Critical Care Medicine 2008;10:278-84.
58. Cooke CR, Hotchkin DL, Engelberg RA, Rubinson L, Curtis JR. Predictors of time to death after terminal withdrawal of mechanical ventilation in the ICU. Chest 2010;138:289-97.
59. de Groot YJ, Lingsma HF, Bakker J, Gommers DA, Steyerberg E, Kompanje EJ. External validation of a prognostic model predicting time of death after withdrawal of life support in neurocritical patients. Critical care medicine 2012;40:233-8.
60. DeVita MA, Brooks MM, Zawistowski C, Rudich S, Daly B, Chaitin E. Donors after cardiac death: validation of identification criteria (DVIC) study for predictors of rapid death. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons 2008;8:432-41.
61. Portenoy RK, Sibirceva U, Smout R, et al. Opioid use and survival at the end of life: a survey of a hospice population. Journal of pain and symptom management 2006;32:532-40.
62. Rabinstein AA, Yee AH, Mandrekar J, et al. Prediction of potential for organ donation after cardiac death in patients in neurocritical state: a prospective observational study. Lancet neurology 2012;11:414-9.
63. Suntharalingam C, Sharples L, Dudley C, Bradley JA, Watson CJ. Time to cardiac death after withdrawal of life-sustaining treatment in potential organ donors.

American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons 2009;9:2157-65.
64. Yee AH, Rabinstein AA, Thapa P, Mandrekar J, Wijdicks EF. Factors influencing time to death after withdrawal of life support in neurocritical patients. Neurology 2010;74:1380-5.
65. Zawistowski CA, DeVita MA. A descriptive study of children dying in the pediatric intensive care unit after withdrawal of life-sustaining treatment. Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies 2004;5:216-23.
66. Wind J, Snoeijs MG, Brugman CA, et al. Prediction of time of death after withdrawal of life-sustaining treatment in potential donors after cardiac death*. Critical care medicine 2012;40:766-9.

A2. b: DePPaRT Protocol (APPENDIX 2b)

Death Prediction and Physiology after Removal of Therapy

Prediction of Time to Death and Description of Physiologic Function During the Dying Process following Withdrawal of Life-Sustaining Therapy: An Observational Study

Case Report Form

DEATH PREDICTION & PHYSIOLOGY AFTER REMOVAL OF THERAPY

DEPPART

ONCE PAPER CASE REPORT FORM IS COMPLETE, PLEASE ENTER ELECTRONICALLY: *www.deppart.org
PLEASE RETAIN ORIGINAL CASE REPORT FORMS
For inquiries, please contact:

Amanda van Beinum
CHEO Central Research Coordinator

E: avanbeinum@cheo.on.ca
T: 613-737-7600 ext.4007
Children's Hospital of Eastern Ontario
Research Institute

CRF Completion Instructions:
Section 1. "Enrollment Criteria"

1.1 Inclusion Criteria:

Check "**yes**" for each inclusion criteria present. **NOTE**: all inclusion criteria must be checked "**yes**" in order for the patient to be eligible for the study.

Consensual decision for WLST means that the family and bedside care team have mutually agreed on this course of action.

Anticipation of imminent death means that bedside care team and family suspect that the planned removal of one or more invasive therapies currently used to sustain life will result in imminent death (e.g. within several hours).

1.2 Exclusion Criteria:

Check "**no**" for each exclusion criteria NOT present. **NOTE**: all exclusion criteria must be checked "no" in order for the patient to be eligible for the study.

NDD – patients are excluded if a formal declaration of neurological death has occurred. If NDD is suspected but no formal testing is done (or formal testing not possible due to injury), this exclusion criteria *would not* apply.

Pacemaker - patients are excluded if they have a functioning pacemaker that remains on at any point during the patient's participation in the study (from 15 minutes prior to WLST to 30 minutes after declaration of death, or 5 minutes for DCD patients).

1.3 Signing of Consent Form:

Check "yes" or "no" and record date. Record the time of consent if this is available. "Waived consent" option for sites with prior central site and REB approval only.

1.4 Agree to Contact for Qualitative Study
(only for centres participating in the qualitative component) :

Check "yes" or "no" for ability to approach surrogate decision maker or legal guardian 4-6 months post-death.

If "yes", please record the contact information (name, home and cell phone, address, and email) of the surrogate decision maker or legal guardian and their relationship to the patient.

GENERAL CRF INSTRUCTIONS:

At the top of each page, enter your Centre number and the Subject's number.

- Enter dates in the format dd/mmm/yyyy (i.e. 22/OCT/2015)
- Enter times according to the 24 hour clock in the format HH:MM (i.e. 4pm is entered 16:00)
- If data is not applicable, not known, illegible, or incorrect, enter N/A. **There should be no blank spaces**

If you enter a value and realize that it is incorrect, please put a line through it, date and initial it and enter the correct value.
EXAMPLE: ~~1 5 0 . 0 0~~ 175.00 RW

***Once the paper form is complete, please enter it electronically at www.deppart.org '**

1. ENROLLMENT CRITERIA

1.1 INCLUSION CRITERIA: (all inclusion criteria must be answered "YES" to include patient)

Admission to ICU	☐YES	☐NO
Corrected gestational age ≥ 1 month	☐YES	☐NO
A consensual decision for the withdrawal of life sustaining therapy (WLST) has been made and there is an anticipation of imminent death	☐YES	☐NO

Subjects will have the following minimum bedside monitors in place:

a. Pulse oximeter plethysmography	☐YES	☐NO
b. Continuous 3-lead electrocardiogram	☐YES	☐NO
c. Invasive arterial blood pressure monitoring	☐YES	☐NO

1.2 EXCLUSION CRITERIA: (all exclusion criteria must be answered "NO" to include patient)

Declared dead by NDD criteria	☐YES	☐NO
ICU physician or member of the bedside healthcare team refusal	☐YES	☐NO
Surrogate decision maker or legal guardian refusal or unavailable to obtain consent	☐YES	☐NO
Has an external or implantable pacemaker and is being paced	☐YES	☐NO

1.3 SIGNING OF CONSENT FORM:

Consent form signed?	☐Yes	☐ No	☐ Waived consent (approved sites only)
Date of consent (dd/mmm/yyyy):	____/_____/_____	Time of Consent (hh:mm)	__ __ : __ __ ☐ Not collected

1.4 AGREE TO CONTACT FOR APPROACH 4-6 MONTHS POST-DEATH?

☐ **N/A – Site not participating in qualitative sub-study**

Did surrogate decision maker or legal guardian agree to a follow up phone call and potential participation in the qualitative study 4-6 months post death? ☐YES ☐NO

If YES, please enter the following information:

Name of Substitute Decision Maker (SDM):

Relationship to patient:

Home and cellphone number of SDM — Home #: Cellphone #:

Address of SDM:

Email:

CRF Completion Instructions:
Section 2. "General Demographic and Baseline Information"

2.1 General Demographics and Baseline Information:

2.1.1 Age: Record the age of the patient in years and/or months.
EXAMPLE: If patient is 6 months old, enter 0 0 Years 0 6 Months.
EXAMPLE: If patient is 76 years old, enter 7 6 Years 0 0 Months.

2.1.2 Date of Patient Enrollment: Enter the date of patient enrollment.

2.1.3 and 2.1.4 Admission to ICU date and time: This is the date and time the patient arrives at the ICU of the study site.

2.1.5 Gender: Select either male or female.

2.1.6 Height: Enter the patient's height in centimeters, or N/A if unavailable.

2.1.7 Weight: Enter the patient's weight in kilograms, or N/A if unavailable.

2.1.8 Admission Diagnosis: Record the patient's admission diagnosis in consultation with the Attending Physician.

2.1.9 and 2.1.10 Chronic pre-existing medical condition(s): This is defined as any condition that requires ongoing follow-up by a specialist, and/or recurrent hospitalization as per the list provided. Check Yes or No for each item. If none, check N/A.

GENERAL CRF INSTRUCTIONS:

At the top of each page, enter your Centre number and the Subject's number.

- Enter dates in the format dd/mmm/yyyy (i.e. 22/OCT/2015)
- Enter times according to the 24 hour clock in the format HH:MM (i.e. 4pm is entered 16:00)
- If data is not applicable, not known, illegible, or incorrect, enter N/A. **There should be no blank spaces**

If you enter a value and realize that it is incorrect, please put a line through it, date and initial it and enter the correct value.
EXAMPLE: ~~1 5 0 . 0 0~~ 175.00 RW

***Once the paper form is complete, please enter it electronically at www.deppart.org**

2. General Demographic and Baseline Information

2.1.1 Age: __ __ Years __ __ Months

2.1.2 Date of Patient Enrollment: |__|__| |__|__|__| | 2 | 0 | 1 |__|
D D / M M M / Y E A R

2.1.3 Admission to ICU date: |__|__| |__|__|__| | 2 | 0 | 1 |__|
D D / M M M / Y E A R

2.1.4 Admission to ICU time: |__|__|*HH :* |__|__| *MIN*

2.1.5 Gender: |__| *Male* |__|*Female*

2.1.6 Height: |__|__|__|*cm*

2.1.7 Weight: |__|__|__|.|__| *kg*

2.1.8 Admission Diagnosis: _____

2.1.9 Chronic pre-existing medical condition? |__| *yes* |__| *no*

2.1.10 If yes to 2.1.9, indicate medical condition (check YES or NO for each item)

☐ N/A (If "NO" to 2.1.9 above)

Chromosomal abnormality	☐YES	☐NO
Neurologic disease	☐YES	☐NO
Chronic Lung disease	☐YES	☐NO
Endocrine disease	☐YES	☐NO
GI disease	☐YES	☐NO
Renal disease	☐YES	☐NO
Musculo-skeletal disease	☐YES	☐NO
Cardiovascular disease	☐YES	☐NO
Rheumatological disease	☐YES	☐NO
Inborn error of metabolism	☐YES	☐NO
Cancer / Oncologic disease	☐YES	☐NO
Psychiatric disorder	☐YES	☐NO
Developmental delay	☐YES	☐NO
Chronic infection	☐YES	☐NO
Immunocompromised	☐YES	☐NO
Other: Specify: _____	☐YES	☐NO

Did patient have cardiac arrest with resuscitation measures within the past 24 hours?	☐YES	☐NO

CRF Completion Instructions:
Section 3. "DCD Eligibility Criteria"

Please complete this form for all subjects enrolled in the DePPaRT study.
3.1 DCD Exclusionary Criteria: If subject is in an institution that does NOT perform DCD and the subject has any of the following, they are considered to be NOT eligible for DCD.

Please indicate **"yes"** or **"no"** to the list of exclusionary items.

3.2 DCD Extended Criteria: Provincial practice warrants further investigation before excluding a potential DCD patient. Donation may still occur under 'extended' DCD criteria. Thus, for our study, if the subject is in an institution that does NOT perform DCD, the below criteria will be included as DCD-eligible

Please indicate **"yes"** or **"no"** to the listed criteria.

3.3 DCD Eligibility by Organ Donation Organization (ODO):

Please indicate **"yes", "no",** or **"not assessed"** for **section 3.3**. Provide reason for ODO assessment of ineligibility. If reason for ODO classification not known, please indicate reason as "unknown".

GENERAL CRF INSTRUCTIONS:

At the top of each page, enter your Centre number and the Subject's number.

- Enter dates in the format dd/mmm/yyyy (i.e. 22/OCT/2015)
- Enter times according to the 24 hour clock in the format HH:MM (i.e. 4pm is entered 16:00)
- If data is not applicable, not known, illegible, or incorrect, enter N/A. **There should be no blank spaces**

If you enter a value and realize that it is incorrect, please put a line through it, date and initial it and enter the correct value.
EXAMPLE: ~~1 5 0 . 0 0~~ 175.00 RW

***Once the paper form is complete, please enter it electronically at www.deppart.org**

3. DCD ELIGIBILITY CRITERIA

3.1 DCD Exclusionary Criteria – does the patient meet any of the following criteria?

>79 years of age	☐YES	☐NO
Active or remote Melanoma	☐YES	☐NO
Active malignancy	☐YES	☐NO
Metastatic malignancy or high grade brain tumour	☐YES	☐NO
Serious unresolved sepsis or systemic infection	☐YES	☐NO
Intravenous drug abuse	☐YES	☐NO
Human T-cell leukemia-lymphoma virus	☐YES	☐NO
Systemic viral infection (measles, rabies, etc)	☐YES	☐NO
Prion related disease	☐YES	☐NO
Herpetic meningoencephalitis	☐YES	☐NO

3.2 DCD Extended Criteria – does the patient meet any of the following criteria?

Bacteremia alone	☐YES	☐NO
Non-melanoma skin malignancies	☐YES	☐NO
Primary non-metastatic brain tumours	☐YES	☐NO
Documented hepatitis B or C	☐YES	☐NO
Documented HIV	☐YES	☐NO

3.3 DCD Eligibility Assessment by Organ Donor Organization (ODO):

Subject was deemed eligible for DCD by local ODO:

☐YES

☐NO (Reason:_____)

☐NOT ASSESSED

CRF Completion Instructions:
Section 4. "Patient Group Assignment"

4.1 Patient Group Assignment: This is defined by the patient criteria. Subject's eligibility for DCD is as per ODO assessment (section 3.1) or as per sections 3.2 and 3.3

GROUP 1: DCD Non-Eligible
GROUP 2: DCD Eligible (but does not progress to organ procurement)
GROUP 3: DCD Patient (progresses to organ procurement)

Please indicate patient group assignment by checking the boxes for the DCD grouping of the patient.

If the patient was eligible for donation but was not approached by the ODO for consent for DCD, please complete 4.1.2.1.

If the patient was eligible for DCD and consent was obtained, but the patient did not proceed to organ procurement, please complete 4.1.3.1.

GENERAL CRF INSTRUCTIONS:

At the top of each page, enter your Centre number and the Subject's number.

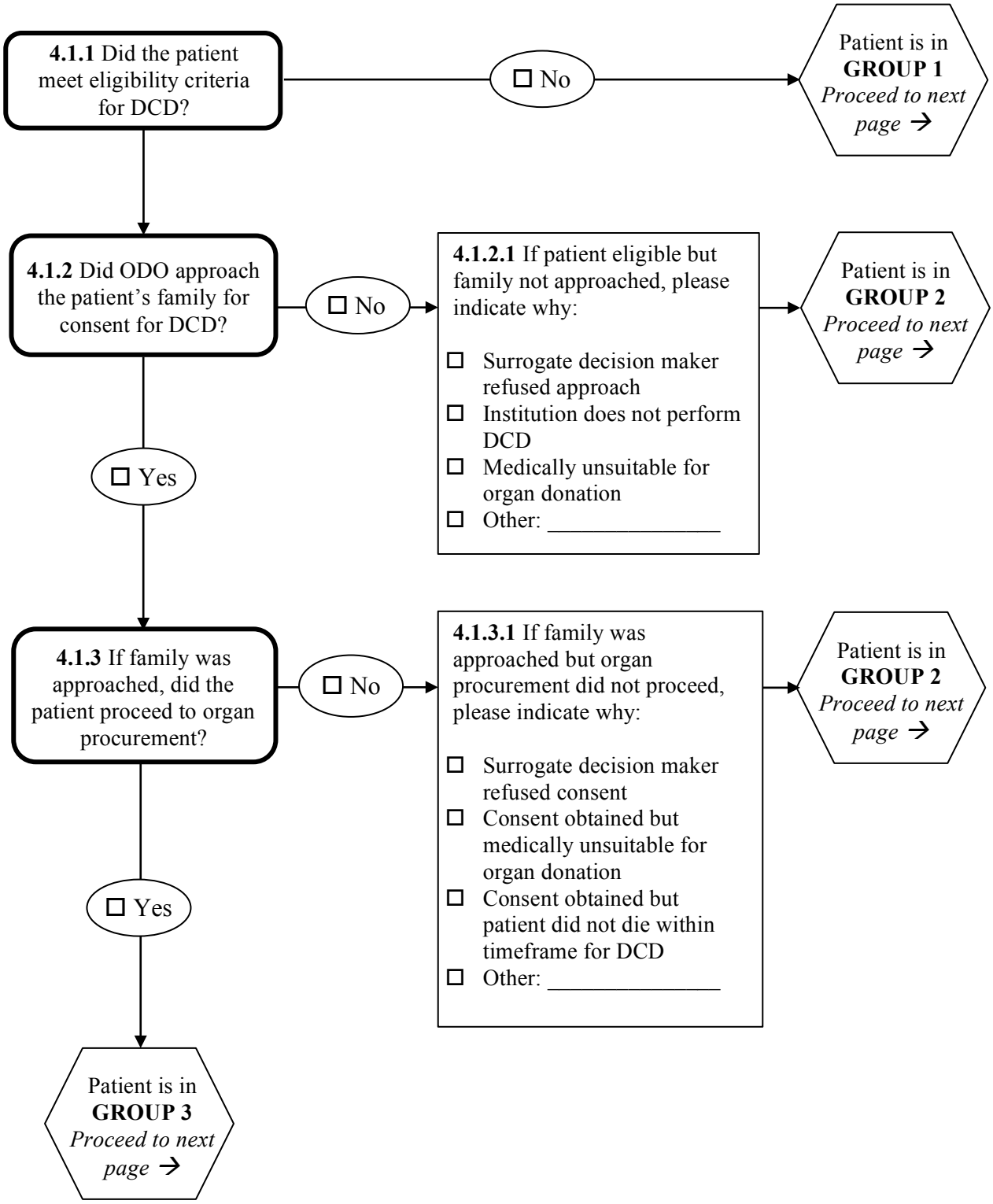
- Enter dates in the format dd/mmm/yyyy (i.e. 22/OCT/2015)
- Enter times according to the 24 hour clock in the format HH:MM (i.e. 4pm is entered 16:00)
- If data is not applicable, not known, illegible, or incorrect, enter N/A. **There should be no blank spaces**

If you enter a value and realize that it is incorrect, please put a line through it, date and initial it and enter the correct value.
EXAMPLE: ~~1 5 0 . 0 0~~ 175.00 RW

***Once the paper form is complete, please enter it electronically at www.deppart.org**

4.1 PATIENT GROUP ASSIGNMENT

Please check all appropriate boxes to indicate patient group assignment. DCD eligibility is as determined in Section 3.0



CRF Completion Instructions:
Section 5. "PRISM III Worksheet"

GENERAL INSTRUCTIONS

- **Only to be completed for pediatric patients**
- **Use data recorded within the first 12 hours of PICU admission.**
- Circle units where appropriate in the "Units" column.

A. Cardiovascular Data (Systolic BP, Heart Rate and Temperature).

Do not use data collected when the child is crying or agitated.

a) Systolic BP

- Use data from an arterial line if available and functioning. Use data collected by a cuff if arterial line not available or if not functioning properly (i.e. dampened waveform).
- Generally, a cardiac arrest involves more than 30 seconds of cardiac massage. For resuscitation with chest compressions and absent blood pressure, record the systolic blood pressure as "0".

b) Heart Rate

- For resuscitation with chest compressions and asystole, record the heart rate as "0".

c) Temperature

- Use rectal, oral, blood, ear (tympanic) or other site known to be close to core temperature. DO NOT USE SKIN TEMPERATURE (i.e. axillary).

B. Acid-Base/Blood Gases Data (pH, PaO_2, and PCO_2)

- Use data from the respiratory flow sheets or directly from laboratory reports.
- Only use arterial blood gas results for PaO_2 values.
- pH and PCO_2 may be obtained from arterial, venous, or capillary blood gas samples.
- Do not use PCO_2 samples obtained during brain death apnea testing.

C. Chemistry Tests (Potassium, Bicarbonate [Total CO_2], Blood Urea Nitrogen [BUN], Creatinine, Glucose)

- Use data obtained directly from the laboratory reports.
- Do not use values from hemolyzed specimens.
- Total CO_2 is obtained from the measured sample (done with electrolytes) and NOT the blood gases. However, if your laboratory does not calculate the measured Total CO_2, use the Bicarbonate value from the blood gas.

D. Hematology Tests (WBC Count, PT, PTT, Platelet Count)

- Indicate whether the actual value is PT or PTT. Do not use INR values.

SEE STUDY PROCEDURES MANUAL FOR FURTHER INFORMATION

5. PRISM III Worksheet – Complete for Pediatric Patients Only

☐ **N/A - Patient is not admitted to PICU (> 18 years)**

Use values obtained within the first 12 hours of PICU admission

***Circle units where appropriate**

Lowest Systolic BP: __ __ __mmHg Highest Heart Rate: __ __ __ bpm

Lowest Temperature: __ __ . __ ^{0}C or N/A ☐ Route (circle one): PR PO Tymp Axillary Esoph Bladder

Highest Temperature: __ __ . __ ^{0}C or N/A ☐ Route (circle one): PR PO Tymp Axillary Esoph Bladder

Pupillary Reflexes: 1 Fixed & Dilated ☐ Both Fixed & Dilated ☐ Other ☐ N/A ☐

Lowest GCS: __ __ or N/A ☐

Lowest pH: __ . __ __ or N/A ☐ Highest pH: __ . __ __ or N/A ☐

Lowest Total $C0_2$ (HCO3): __ __ . __ or N/A ☐ Highest Total $C0_2$ (HCO3): __ __ . __ or N/A ☐

Lowest PaO_2: __ __ __ . __ mmHg or N/A ☐

Highest $PaCO_2$: __ __ __ . __ mmHg or N/A ☐

Highest Glucose*: __ __ . __ mmol/L OR md/gL or N/A ☐

Highest K+: __ . __ mmol/L or N/A ☐

Highest Creatinine*: __ __ __ . __ µmol/L OR mg/dL or N/A ☐

Highest BUN*: __ __ . __ mmol/L OR mg/dL or N/A ☐

Lowest WBC: __ __ . __ $X10^9$/L or N/A ☐

Highest PT or PTT*: __ __ __ . __ PT OR PTT or N/A ☐

Lowest Platelet Count: __ __ __ __ . __ X 10^9/L or N/A ☐

CRF Completion Instructions: Section 5. "APACHE II Worksheet"

A. GENERAL INSTRUCTIONS FOR PHYSIOLOGIC VARIABLES

- **Only to be completed for adult patients**
- All APACHE II **data collected must be from the first 24 hours following ICU admission**. The GCS assessment should be taken prior to the patient receiving sedation. This may be outside of the 24-hour assessment period but will provide a more accurate score of neurological function.
- When recording variables for the Acute Physiology Score, if a physiologic measurement is not obtained during the 24 hour time frame, assign a zero ("0") point score.
- For all acute physiologic measurements: choose the *worst, most abnormal value* recorded during the full 24-hour assessment period. These values may be low or high, but will always be the most deranged value with the highest point score (furthest away from the column headed 0-Normal). Remember that this data is not compared to local laboratory values but rather the APACHE II scoring system.
- Do not include values from the Operating Room.
- Do not include values you assess as being transient (e.g. a 1 time spike or drop in blood pressure).

Temperature

- Record rectal or core temperature in degrees Celsius (°C).
- Add 0.5°C if oral.
- Add 1.0°C if axillary.

Mean Arterial Pressure (MAP)

- Record in mmHg.
- Use the following formula to calculate the MAP: SBP+[DBP×2] ÷ 3.

Heart Rate

- Do not score for bradycardia if a pacemaker is present.
- Record the documented ventricular rate.

Respiratory Rate

- Record the most deranged ventilated or non-ventilated rate.

Oxygenation

- If the patient has an $FiO_2 < 0.5$ **AND** ≥ 0.5 within this same 24-hour period, use the $AaD0_2$ or $Pa0_2/Fi0_2$ value which scores highest in this category.
- The formula to calculate $AaD0_2$ at sea level is: $[FiO_2 \times 713]-[PaCO_2 \div 0.8]- PaO_2$
- Please refer to your hospital laboratory for local barometric pressures because this impacts the value that should be used for accurate calculations. If you are at sea level (an altitude less than 1000 feet) use a barometric pressure of 760 mmHg minus the pressure of water (47 mmHg) for a total pressure of 713 mmHg.

C. CHRONIC HEALTH DEFINITIONS

Organ insufficiency or immunocompromised state evident prior to this hospital admission and are consistent with the following criteria:

LIVER: Biopsy-proven cirrhosis and documented portal hypertension; prior episodes of upper GI bleeding attributed to portal hypertension; or prior episodes of hepatic failure/encephalopathy/coma.

CARDIOVASCULAR: New York Heart Association Class IV.

RESPIRATORY: Chronic restrictive, obstructive, or vascular disease resulting in severe exercise restriction (i.e., unable to climb stairs or perform activities of daily living or household duties; or documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension (>40 mmHg), or ventilator dependency.

RENAL: Receiving chronic dialysis.

IMMUNO-COMPROMISED: The patient has received therapy that suppresses resistance to infection (i.e., immuno-suppressive treatment, chemotherapy, radiation, long term or recent high dose steroids, or has a disease that is sufficiently advanced to suppress resistance to infection (i.e., leukemia, lymphoma, AIDS).

6. APACHE II WORKSHEET – COMPLETE FOR ADULT PATIENTS ONLY

☐ **N/A - Patient is not admitted to an Adult ICU (< 18 years)**

A. Physiologic Variables Points

PHYSIOLOGIC VARIABLE	HIGH ABNORMAL RANGE					LOW ABNORMAL RANGE				PT SCORE
	4	3	2	1	0	1	2	3	4	
Temperature - rectal (°C)	≥ 41	39-40.9		38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	≤ 29.9	
MAP (mmHg)	≥ 160	130-159	110-129		70-109		50-69		≤ 49	
Heart Rate	≥ 180	140-179	110-139		70-109		55-69	40-54	≤ 39	
Respiratory Rate (non-ventilated or ventilated)	≥ 50	35-49		25-34	12-24	10-11	6-9		≤ 5	
Oxygenation: [A-aDO_2 = (FiO_2 x 710) – (PCO_2 x 1.25) – PO_2]					FiO_2 =		PCO_2 =		PO_2 =	
a. FiO_2 ≥ 0.5 record A-aDO_2	≥ 500	350-499	200-349		< 200					
b. FiO_2 < 0.5 record only PaO_2					PO_2 > 70	PO_2 61-70		PO_2 55-60	PO_2 < 55	
Arterial pH	≥ 7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	< 7.15	
Serum Na (mmol/L)	≥ 180	160-179	155-159	150-154	130-149		120-129	111-119	≤ 110	
Serum K (mmol/L)	≥ 7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		< 2.5	
Serum Creatinine (umol/L)	> 305	170-304	130-169		53-129		<53			
Hematocrit (%)	≥ 60		50-59.9	46-49.9	30-45.9		20-29.9		< 20	
WBC (total/mm^3)	≥ 40		20-39.9	15-19.9	3-14.9		1-2.9		< 1	
Glasgow Coma Score (GCS)	Score = 15 minus actual GCS (see below)									
Serum HCO_3 (venous mmol/L) - not preferred, use if no ABG's	≥ 52	41-51.9		32-40.9	22-31.9		18-21.9	15-17.0	< 15	
Creatinine double points for ACUTE Renal Failure	ACUTE PHYSIOLOGY SCORE (APS): Sum of the 12 individual variable points =									

B. Age Points - Assign points to age as follows:

AGE (yrs)	POINTS
< 44	0
45-54	2
55-64	3
65-74	5
≥ 75	6
AGE SCORE =	

C. Chronic Health Points - **If the patient has a history of severe organ system insufficiency (see opposite) or is immunocompromised assign points as follows:**

a. For nonoperative or emergency postoperative pt -- 5 points
b. For elective postoperative pt -- 2 points

CHRONIC HEALTH SCORE = ____

D. GLASGOW COMA SCALE

Parameter	Response	Points Assigned (please circle)
Eyes Open	Spontaneously	4
	On spoken command	3
	On pain	2
	No response	1
Best Motor Response	To spoken command	6
	To painful stimulus:	
	Localized pain	5
	Flexion withdrawal	4
	Flexion abnormal	3
	Extension	2
	No response	1
Best Verbal Response If intubated: Appears to be able to converse = 5 Ability to converse questionable = 3 Unresponsive = 1		
	Oriented & converses	5
	Disoriented & converses	4
	Inappropriate words	3
	Incomprehensible sounds	2
	No response	1
	TOTAL GCS =	

E. APACHE II SCORE - Sum of A + B + C

A. APS points	
B. Age points	
C. Chronic Health points	
APACHE II SCORE =	

CRF Completion Instructions:
Section 7. "CT Scan (Head) and Marshall Score"

Only to be completed for patients who have had a CT head scan prior to WLST.

SPECIFIC INSTRUCTIONS
Please review with your site investigator/radiologist the CT scan and radiology report to complete the "CT Scan (Head) and Marshall Score Form". Please enter the data from this form in the section below.

Check boxes where appropriate.

7.1.1 Date of CT Scan: Use CT report for the CT scan performed closest to time of WLST. **Date and time of initiation of WLST is when the FIRST action to begin WLST occurs.** As example, extubation, weaning/stopping of vasopressors or weaning/stopping of the ventilator settings.

7.1.2 CT Scan (Head): Please ensure to retain a copy of the CT scan report with the patient's Case Report Form.

Check "Right", "Left", or both accordingly. If none of the listed conditions were present, please check "Not Present". If the research coordinator and the physician/radiologist are unsure, please check "unknown".

7.1.3 Marshall Score: Data on brain CT images will be collected according to the presence or absence of specified lesions. The Marshall score classifies the lesions into six categories.

Please document the Marshall Score based on the CT scan performed closest to time of WLST. Please review the CT scan with your investigator/radiologist.

GENERAL CRF INSTRUCTIONS:

At the top of each page, enter your Centre number and the Subject's number.

- Enter dates in the format dd/mmm/yyyy (i.e. 22/OCT/2015)
- Enter times according to the 24 hour clock in the format HH:MM (i.e. 4pm is entered 16:00)
- If data is not applicable, not known, illegible, or incorrect, enter N/A. **There should be no blank spaces**

If you enter a value and realize that it is incorrect, please put a line through it, date and initial it and enter the correct value.
EXAMPLE: ~~1 5 0 . 0 0~~ 175.00 RW

***Once the paper form is complete, please enter it electronically at www.deppart.org**

7. CT HEAD AND MARSHALL SCORE

☐ N/A- CT scan not performed prior to WLST.

7.1.1 Date of Initiation of CT Scan: |__|__| |__|__|__| | 2 | 0 | 1 |__|

7.1.2 CT Scan - Type of intracranial injuries seen (check ALL that apply)

	Left	Right	Not Present	Unknown
Hematoma (subdural or epidural)	☐	☐	☐	☐
Brain/intracerebral/intraventricular contusion/hemorrhage	☐	☐	☐	☐
Subarachnoid hemorrhage	☐	☐	☐	☐
Cerebral edema	☐	☐	☐	☐
Brain tumour	☐	☐	☐	☐
Infection (meningitis/encephalitis/space occupying lesion)	☐	☐	☐	☐
External ventricular device	☐	☐	☐	☐
Decompressive craniectomy	☐	☐	☐	☐
Other (please specify/describe):				

7.1.3 Marshall Score – Select the injury classification for this patient (select only ONE classification based on data available)

☐ Please check if patient had a Traumatic brain injury

Marshall Injury Class	Class Description
☐ Diffuse injury I	No visible intracranial pathology
☐ Diffuse injury II	Cisterns are present with midline shift of 0-5mm and/or lesion densities present, no high or mixed density lesion at >=25mL
☐ Diffuse injury III	Cisterns compressed or absent, with midline shift of 0-5mm, no high or mixed density lesion at >=25mL
☐ Diffuse injury IV	Midline shift of >5mm, no high or mixed density lesion at >=25mm
☐ Diffuse injury V	Any lesion surgically evacuated
☐ Diffuse injury VI	High or mixed density lesion of >=25mL, not surgically evacuated

CRF Completion Instructions:
Section 8. "Prediction of Time to Death"

Prior to WLST, the research coordinator will ask the Most Responsible Physician and bedside nurse their medical opinion in regard to prediction of time to death once life support is removed. One or both healthcare team providers are invited to respond. Refusal or inability to respond is to be documented.

Please record all information from the "Prediction of Time to Death Form".

GENERAL CRF INSTRUCTIONS:

At the top of each page, enter your Centre number and the Subject's number.

- Enter dates in the format dd/mmm/yyyy (i.e. 22/OCT/2015)
- Enter times according to the 24 hour clock in the format HH:MM (i.e. 4pm is entered 16:00)
- If data is not applicable, not known, illegible, or incorrect, enter N/A. **There should be no blank spaces**

If you enter a value and realize that it is incorrect, please put a line through it, date and initial it and enter the correct value.
EXAMPLE: ~~1 5 0 . 0 0~~ 175.00 RW

***Once the paper form is complete, please enter it electronically at www.deppart.org**

8. PREDICTION OF TIME TO DEATH

***** ORIGINAL FORM MUST BE COMPLETED BY THE MOST RESPONSIBLE PHYSICIAN AND BEDSIDE NURSE PRIOR TO WLST*****

8.1.1 Did the Most Responsible Physician complete the prediction of time to death?

- ☐ Yes
- ☐ No
- ☐ Refusal to Predict Time to Death
- ☐ Other: _____

If YES, please indicate prediction and strength of certainty (pick one):

A. Death will occur within:
- ☐ 1 hour of WLST?
- ☐ 2 hours of WLST?
- ☐ 3 hours of WLST?
- ☐ 6 hours of WLST?

B. How certain are you that death will occur within this time period? ☐ Low ☐ Moderate ☐ High

Time of Completion of Form: |__|__|*HH :* |__|__| *MIN*
Date of Completion of Form: |__|__| |__|__|__| | 2 | 0 | 1 |__|

Comments:_____
_____

8.1.2 Did the bedside nurse complete the prediction of time to death?

- ☐ Yes
- ☐ No
- ☐ Refusal to Predict Time to Death
- ☐ Other: _____

If YES, please indicate prediction and strength of certainty (pick one):

A. Death will occur within:
- ☐ 1 hour of WLST?
- ☐ 2 hours of WLST?
- ☐ 3 hours of WLST?
- ☐ 6 hours of WLST?

B. How certain are you that death will occur within this time period? ☐ Low ☐ Moderate ☐ High

Time of Completion of Form: |__|__|*HH :* |__|__| *MIN*
Date of Completion of Form: |__|__| |__|__|__| | 2 | 0 | 1 |__|

Comments:_____
_____

CRF Completion Instructions:
Section 9. "Withdrawal of Life Sustaining Therapy (WLST)"

9.1 – 9.3 Metrics of patient volume: record the number of staffed beds, ventilated patients, and bedside nurses in the ICU at the time of WLST for each enrolled patient.

9.4 & 9.5 Blood gas and lactate: record the values from the last blood gas and last lactate done prior to the start of WLST, and the date and time that they were measured. If no blood gas or lactate, check "No".

9.6 & 9.7 Date and time of initiation of WLST: Date and time of initiation of WLST is when the FIRST action to begin WLST occurs. As example, extubation, weaning/stopping of vasopressors or weaning/stopping of the ventilator settings**.**

EXAMPLE: For patient X, the process of WLST involves stopping all vasoactive medications at 13:00 and extubation at 13:03. The first action of WLST is the stopping of vasoactive medications. For this patient, WLST was initiated at 13:00.

9.8 First Action of WLST: Select the first action of WLST as performed for this patient. While it is possible multiple actions are ordered at the time of WLST, please indicate the "action" which was started first

9.9 Vital Signs: Record the blood pressure (BP), mean arterial pressure (MAP), pulse rate, respiratory rate (RR), and Glasgow Coma Score (GCS) at the time of initiation of WLST. If no measures are available at the time of WLST, use the closest values available *prior to start of WLST.*

9.10 Extubation: record the date and time of extubation if the patient was extubated prior to death. Ensure that an accurate record of all interventions and respiratory settings (e.g. FiO_2 levels) after WLST are recorded in section 15.

9.11 Reflexes: Record reflexes at the last neurological exam prior to WLST. Please record the date and time of the exam.

GENERAL CRF INSTRUCTIONS:

At the top of each page, enter your Centre number and the Subject's number.

- Enter dates in the format dd/mmm/yyyy (i.e. 22/OCT/2015)
- Enter times according to the 24 hour clock in the format HH:MM (i.e. 4pm is entered 16:00)
- If data is not applicable, not known, illegible, or incorrect, enter N/A. **There should be no blank spaces**

If you enter a value and realize that it is incorrect, please put a line through it, date and initial it and enter the correct value.

EXAMPLE: ~~1 5 0 . 0 0~~ 175.00 RW

***Once the paper form is complete, please enter it electronically at www.deppart.org**

9. WITHDRAWAL OF LIFE SUSTAINING THERAPY (WLST)

At the time of WLST, please indicate the number of:

9.1 Staffed ICU beds: __ __ **9.2** Ventilated patients: __ __ **9.3** Bedside nurses: __ __

9.4 Did the patient have a blood gas done at any time prior to WLST?

☐ **No** ☐ **Yes** *(please record the following)*: ☐ **Venous gas** ☐ **Arterial gas**

Date of gas (*DD/MMM/YYYY*): __ __ / __ __ __ / __ __ __ __ **Time of gas *(HH:MM):*** __ __ : __ __ __ __

pH: __ . __ __ **PaO2:** __ __ . __ __ **PCO2:** __ __ __ . __ __

9.5 Did the patient have lactate levels measured at any time prior to WLST? ☐ **No**

☐ **Yes** *(please record the following)*:

Date of measure (*DD/MMM/YYYY*): __ __ / __ __ __ / __ __ __ __ Time of measure *(HH:MM):* __ __ : __ __ __ __ **Lactate:** __ __ __ . __ __

9.6 Time of Initiation of WLST: |__|__| ***HH :*** |__|__| ***MIN***

9.7 Date of Initiation of WLST: |__|__|/|__|__|__| /| **2** | **0** | **1** |__|

9.8 What is the first action of WLST performed? (please select the FIRST therapy removed)

☐ Reduction in vasoactive drug dose or infusion number	☐ Reduction in ventilator settings (rate, FiO_2%, volume, etc.)
☐ Extubation (removal of endotracheal tube)	☐ Change in ventilator mode (switch to non-invasive ventilation, T-piece, etc.)
☐ Other: _____	

9.9 Record Vital Signs at time initiation of WLST:

BP (S/D): __ __ __ / __ __ __ MAP: __ __ __ Pulse (bpm): __ __

RR (rate/min): __ __ GCS: Eyes __ Motor __ Verbal __

9.10 Was the patient extubated (removal of ETT) prior to the declaration of death?

☐ **No** *(please record all respiratory interventions/settings in section 12)*

☐ **Yes** *(please record the following, in addition to completing section 12)*:

Date of Extubation (DD/MMM/YYYY): __ __ / __ __ __ / __ __ __ __

Time of Extubation (HH:MM): __ __ : __ __ __ __

9.11 Reflexes at time of WLST (Please use most recent neurological exam prior to WLST):

Date of Neurological Exam: |__|__| |__|__|__| | 2 | 0 | 1 |__| ☐ - N/A, No exam done

Time of Neurological Exam: |__|__| : |__|__|

Reflex	Left Side			Right Side		
	Present	Absent	Not Tested	Present	Absent	Not Tested
Pupils	☐	☐	☐	☐	☐	☐
Corneal	☐	☐	☐	☐	☐	☐
Oculovestibular (cold calories)	☐	☐	☐	☐	☐	☐
Oculocephalic	☐	☐	☐	☐	☐	☐
Gag	☐ Present		☐ Absent		☐ Not tested	
Cough	☐ Present		☐ Absent		☐ Not tested	

CRF Completion Instructions:
Section 10. "Interventions From 1 Hour Before WLST Until Death – Circulatory Therapies"

Please use this table to list all circulatory drugs and/or therapies administered **during the one hour prior to WLST until the declaration of death, including all circulatory therapies that were continued and any new therapies started during this time period.**

EXAMPLE: A patient is receiving 5.0 mcg/min (32mcg/mL) of norepinephrine that started at that dose at 08:00 on May 10, 2016, and an infusion of 0.04 units/min (1unit/1mL) of vasopressin that started at that dose at 10:00 on May 10, 2016. At 16:05 on May 12, 2016, the patient is extubated (WLST begins at this time). At the same time as extubation (16:05 on May 12, 2016) the infusion dose of norepinephrine is decreased to 2.0 mcg/min, and the vasopressin is completely stopped. At 16:10 on May 12, 2016, the infusion dose of norepinephrine is completely stopped. No further circulatory therapies are administered, and the patient is declared dead at 16:30 on May 12, 2016. Section 13 for this patient would be completed as follows:

Name of Drug/Therapy	Dose	Units	Concentration	Start date of this dose/therapy	Start time of this dose/therapy	Stop date of this dose/therapy	Stop time of this dose/therapy
norepinephrine	5.0	mcg/min	32 mcg/mL	10/MAY/2016	08:00	12/MAY/2016	16:05
vasopressin	0.04	units/min	1unit/1mL	10/MAY/2016	10:00	12/MAY/2016	16:05
vasopressin	0.0	units/min	1unit/1mL	12/MAY/2016	16:05	12/MAY/2016	16:30
norepinephrine	2.0	mcg/min	32 mcg/mL	12/MAY/2016	16:05	12/MAY/2016	16:10
norepinephrine	0.0	mcg/min	32 mcg/mL	12/MAY/2016	16:10	12/MAY/2016	16:30

If the drug or therapy was administered to the patient any any time in the period from 1 hour prior to WLST until the declaration of death, please provide the following information:

- Start date (DD/MMM/YYYY) and time (HH:MM) of that dose/therapy. Use the start date and time of that specific dose.
- Any changes in the dosage during this time period– complete a new line for each dose
- Record all appropriate units, and drug concentrations (if applicable)
- Please include both continuous infusions and boluses
- Record the stop date (DD/MMM/YYYY) and time (HH:MM) of each dose/therapy. Include a start date and time for the dose of 0.0, to indicate when a drug was completely stopped. If the drug/therapy continues until death, write the date and time of death as the stop time.

Examples of circulatory therapies include but are not limited to: dopamine, ephinephrine, norepinephrine, pheynylephrine, dobutamine, milrinone, nitroglycerin, nitroprusside, labetolol, esmolol, amiodatone, vasopressin, ECMO, intraaortic balloon pumps, ventricular assist devices, and continuous renal replacement therapy.

10. Circulatory Therapies Administered From 1Hr Before WLST Until Death

10.1 Did this patient receive any ionotropes, vasopressors, or other circulatory interventions (e.g. ECMO, SLED) at any time during the period ***from 1 hour prior to WLST until the declaration of death?***

☐ **- No**

☐ **- Yes** (if yes – please indicate which interventions were given using the table below)

Please list all circulatory drugs or therapies patient received from 1 hour prior to WLST until the declaration of death. Examples of circulatory therapies include but are not limited to: dopamine, ephinephrine, norepinephrine, pheynylephrine, dobutamine, milrinone, nitroglycerin, nitroprusside, labetolol, esmolol, amiodatone, vasopressin, ECMO, intraaortic balloon pumps, ventricular assist devices, and continuous renal replacement therapy.

Name of Drug or Therapy	**Dose** *(or NA if not applicable)*	**Units** *(or NA if not applicable)*	**Concentration** *(or NA if not applicable)*	**Start Date of this dose/therapy**	**Start Time of this dose/therapy**	**Stop Date of this dose/therapy**	**Stop Time of this dose/therapy**
				(DD/MMM/YYYY)	(HH:MM)	(DD/MMM/YYYY)	(HH:MM)
	|__|__|__| . |__|__|			__/___/____	__ : __	__/___/____	__ : __
	|__|__|__| . |__|__|			__/___/____	__ : __	__/___/____	__ : __
	|__|__|__| . |__|__|			__/___/____	__ : __	__/___/____	__ : __
	|__|__|__| . |__|__|			__/___/____	__ : __	__/___/____	__ : __
	|__|__|__| . |__|__|			__/___/____	__ : __	__/___/____	__ : __
	|__|__|__| . |__|__|			__/___/____	__ : __	__/___/____	__ : __
	|__|__|__| . |__|__|			__/___/____	__ : __	__/___/____	__ : __
	|__|__|__| . |__|__|			__/___/____	__ : __	__/___/____	__ : __

** Please print and attach additional pages as necessary.*

CRF Completion Instructions:
Section 11. "Interventions From 1 Hour Before WLST Until Death – Neurologic Therapies"

Please use this table to list all neurologic therapies administered **during the one hour prior to WLST until the declaration of death, including all neurologic therapies that were continued and any new therapies started during this time period.**

EXAMPLE: A patient is receiving 0.08 mg/kg/hr of midazolam (1mg/1mL) that started at that dose at 18:30 on May 5, 2016. At 10:10 on May 8, 2016, the patient is given a 5.0 mg bolus of morphine. At 10:20 on May 8, 2016, the patient is extubated (WLST begins at this time). At 10:25, the infusion dose of midazolam is increased to 0.10 mcg/kg/min. At 10:45, the infusion dose of midazolam is again increased to 0.12 mcg/kg/min. At 10:47, the patient is given a 5.0 mg bolus of morphine. No further drugs are given or changes made, and the patient is declared dead at 11:00 on May 8, 2016. Section 14 for this patient would be completed as follows:

Name of Drug/Therapy	Dose	Units	Concentration	Start date of this dose/therapy	Start time of this dose/therapy	Stop date of this dose/therapy	Stop time of this dose/therapy
midazolam	0.08	mg/kg/hr	1mg/1mL	05/MAY/2016	18:30	08/MAY/2016	10:25
morphine	5.0	mg	NA	08/MAY/2016	10:10	08/MAY/2016	10:11
midazolam	0.10	mg/kg/hr	1mg/1mL	08/MAY/2016	10:25	08/MAY/2016	10:45
midazolam	0.12	mg/kg/hr	1mg/1mL	08/MAY/2016	10:45	08/MAY/2016	11:00
morphine	5.0	mg	NA	08/MAY/2016	10:47	08/MAY/2016	10:48

If the drug or therapy was administered to the patient any any time in the period from 1 hour prior to WLST until the declaration of death, please provide the following information:

- Start date (DD/MMM/YYYY) and time (HH:MM) of that dose/therapy. Use the start date and time of that specific dose.
- Any changes in the dosage after the start of WLST – complete a new line for each dose
- Record all appropriate units, and drug concentrations (if applicable)
- Please include both continuous infusions and boluses
- Stop date (DD/MMM/YYYY) and time (HH:MM) of each dose/therapy. **For infusions:** Include a start date and time for the dose of 0.0, to indicate when a drug was completely stopped. If drug/therapy continues until death, write date and time of death as stop time. **For boluses:** Unless stop time is known (e.g. bolus of 5.0 mg morphine over 5 minutes), assume a stop time 1min after the start time.

Examples of neurologic therapies include but are not limited to: morphine, fentanyl, hydromorphone, midazolam, lorazepam, diazepam, clonidine, propofol, pentobarbitol, dexmedetonmidine, cisacurium, rocuronium, and pancuronium.

11. Neurologic Therapies Administered From 1Hr Before WLST Until Death

11.1 Did this patient receive any sedation, analgesia, and/or neuromuscular blockades at any time during the period *from 1 hour prior to WLST until the declaration of death?*

☐ **- No**
☐ **- Yes** (if yes – please indicate which drugs/interventions were given using the table below)

Please list all neurologic therapies (analgesia, sedation, and/or neuromuscular blockades) patient received from 1 hour prior to WLST until the declaration of death. Examples of neurologic therapies include but are not limited to: morphine, fentanyl, hydromorphone, midazolam, lorazepam, diazepam, clonidine, propofol, pentobarbitol, dexmedetonmidine, cisacurium, rocuronium, and pancuronium.

Name of Drug or Therapy	**Dose** *(or NA if not applicable)*	**Units** *(or NA if not applicable)*	**Concentration** *(or NA if not applicable)*	**Start Date of this dose/therapy** (DD/MMM/YYYY)	**Start Time of this dose/therapy** (HH:MM)	**Stop Date of this dose/therapy** (DD/MMM/YYYY)	**Stop Time of this dose/therapy** (HH:MM)
	|__|__|__| . |__|__|			__/___/____	__ __ : __ __	__/___/____	__ __ : __ __
	|__|__|__| . |__|__|			__/___/____	__ __ : __ __	__/___/____	__ __ : __ __
	|__|__|__| . |__|__|			__/___/____	__ __ : __ __	__/___/____	__ __ : __ __
	|__|__|__| . |__|__|			__/___/____	__ __ : __ __	__/___/____	__ __ : __ __
	|__|__|__| . |__|__|			__/___/____	__ __ : __ __	__/___/____	__ __ : __ __
	|__|__|__| . |__|__|			__/___/____	__ __ : __ __	__/___/____	__ __ : __ __
	|__|__|__| . |__|__|			__/___/____	__ __ : __ __	__/___/____	__ __ : __ __
	|__|__|__| . |__|__|			__/___/____	__ __ : __ __	__/___/____	__ __ : __ __
	|__|__|__| . |__|__|			__/___/____	__ __ : __ __	__/___/____	__ __ : __ __

** Please print and attach additional pages as necessary.*

CRF Completion Instructions:
Section 12. " Interventions From 1 Hour Before WLST Until Death – Respiratory Therapies"

Please use the table to record all respiratory therapies (including airway protection and ventilation) **during the one hour prior to WLST until the declaration of death, including all respiratory therapies that were continued and any new therapies started during this time period.** Use the "Route" column to indicate how the patient received therapy (e.g. endotracheal tube (ETT), tracheotomy (Trach), nasal cannula (NC), face mask (FM), etc.)

EXAMPLE: On May 7, 2016 at 17:00, the patient is intubated on conventional mechanical ventilation on CPAP mode with an FiO_2 of 50%. At 13:50 on May 10, 2016, the FiO2% is reduced to 45%. WLST begins at 14:00 on May 10, 2016 when vasopressors are stopped. At 14:05, the FiO_2% is reduced to 30%. At 14:15, the patient is suctioned for respiratory secretions. At 14:20, mechanical ventilation is removed (but the patient remains intubated), and the patient is placed on a T-piece, breathing room air (FiO_2 at 21%). At 14:35, the patient is extubated. The patient is declared dead at 14:45. Section 15 for this patient would be completed as follows:

Respiratory Therapy	Start Date of this therapy	Start Time of this therapy	Route	FiO_2	MPaw	PIP	RR (set)	RR (act.)	PEEP	Stop Date of this therapy	Stop Time of this therapy
CMV on CPAP	07/MAY/2016	17:00	ETT	0.50	NA	NA	20	20	10	10/MAY/2016	13:50
CMV on CPAP	10/MAY/2016	13:50	ETT	0.45	NA	NA	20	20	10	10/MAY/2016	14:05
CMV on CPAP	10/MAY/2016	14:05	ETT	0.30	NA	NA	20	20	10	10/MAY/2016	14:20
T-piece	10/MAY/2016	14:20	ETT	0.21	NA	NA	NA	NA	NA	10/MAY/2016	14:35

Number of times patient was suctioned: 1 **Date and time of last suction prior to death:** 10/MAY/2016 14:15

12.2 Number of times patient suctioned: Record the number of times the patient was suctioned from the time WLST began to the time of declaration of death.

12.3 Last time of suctioning: Record the time the patient was last suctioned prior to declaration of death.

Examples of respiratory therapies include: invasive mechanical ventilation, non-invasive mechanical ventilation, nasopharyngeal airway, face mask, high flow nasal cannula, and T-piece.

12. Respiratory Therapies From 1Hr Before WLST Until Death

12.1 Was this patient intubated, ventilated, or receiving any other respiratory interventions (e.g. face mask, inspired O_2, inspired NO_2) at any time during the period *from 1 hour prior to WLST until the declaration of death?*

☐ - **No**

☐ - **Yes** (if yes – please indicate which interventions were administered using the table below)

Please list all respiratory therapies (including airway protection and ventilation) that the patient received from 1 hour prior to WLST until the declaration of death. Examples of respiratory therapies include: invasive mechanical ventilation, non-invasive mechanical ventilation, nasopharyngeal airway, face mask, high flow nasal cannula, and T-piece.

Respiratory Therapy	Start Date of this therapy	Start Time of this therapy	Route (ETT, Trach, FM, NC, etc.)	FiO_2 (%)	MPaw (cm H_2O)	PIP (cmH_2O)	RR (set)	RR (actual)	PEEP (cmH_2O)	Stop Date of this therapy	Stop Time of this therapy
	(DD/MMM/YYYY)	(HH:MM)								(DD/MMM/YYYY)	(HH:MM)
	__/___/____	__ __:__ __								__/___/____	__ __:__ __
	__/___/____	__ __:__ __								__/___/____	__ __:__ __
	__/___/____	__ __:__ __								__/___/____	__ __:__ __
	__/___/____	__ __:__ __								__/___/____	__ __:__ __
	__/___/____	__ __:__ __								__/___/____	__ __:__ __
	__/___/____	__ __:__ __								__/___/____	__ __:__ __
	__/___/____	__ __:__ __								__/___/____	__ __:__ __
	__/___/____	__ __:__ __								__/___/____	__ __:__ __
	__/___/____	__ __:__ __								__/___/____	__ __:__ __
	__/___/____	__ __:__ __								__/___/____	__ __:__ __
	__/___/____	__ __:__ __								__/___/____	__ __:__ __

12.2 Number of times that patient was suctioned between start of WLST and Declaration of Death: ________________

12.3 Date & time of last suctioning prior to declaration of death:

DATE:__ __ / __ __ __ / __ __ __ __ **TIME:** __ __: __ __

CRF Completion Instructions:
Section 13. "Declaration of Death"

At the time of declaration of death, the research coordinator will ask the Most Responsible Physician to complete the "Checklist for the Declaration of Death".

Answers from this form are to be recorded in the CRF.

A. Who declared death: Indicate who declared death for this patient.

B. Time of Declaration of Death: Record time and date of declaration of death.

C. Diagnostic Tests Used to Determine Death: Using the Declaration of Death Checklist, have the Most Responsible Physician indicate **YES** or **NO** for each of the diagnostic tests listed.

D. "No Touch Time": If your site uses a specific period of observation of diagnostic tests (a "no touch time") as part of the process for declaring death, indicate time period and any other pertinent details.

E. Additional measures to determine death: Indicate what other measures were used to determine death – check **YES** or **NO** for each response.

F. Repeated tests: If tests were repeated, record the number of minutes after the original tests where a repeat test was done. If no repeated tests were done, enter "N/A"

GENERAL CRF INSTRUCTIONS:

At the top of each page, enter your Centre number and the Subject's number.

- Enter dates in the format dd/mmm/yyyy (i.e. 22/OCT/2015)
- Enter times according to the 24 hour clock in the format HH:MM (i.e. 4pm is entered 16:00)
- If data is not applicable, not known, illegible, or incorrect, enter N/A. **There should be no blank spaces**

If you enter a value and realize that it is incorrect, please put a line through it, date and initial it and enter the correct value.
EXAMPLE: ~~1 5 0 . 0 0~~ 175.00 RW

***Once the paper form is complete, please enter it electronically at www.deppart.org**

13. DECLARATION OF DEATH

*****ORIGINAL FORM TO BE COMPLETED BY THE MOST RESPONSIBLE PHYSICIAN AT THE TIME OF DECLARATION OF DEATH*****

A. Who declared death? Please indicate who performed the declaration of death:

- ☐ Most Responsible Physician
- ☐ Fellow
- ☐ Resident
- ☐ Nurse
- ☐ Other: _____

B. Time of Declaration of Death: |__|__|*HH :* |__|__| *MIN*
Date of Declaration of Death: |__|__|/|__|__|__|__|/| 2 | 0 | 1 |__|

C. Specifically, which of the following diagnostic tests were used to determine death after cardiac arrest? (Please check responses below):

Absent heart sounds by auscultation	☐ YES	☐ NO
Absent palpable pulse	☐ YES	☐ NO
Absent pulse by audible Doppler	☐ YES	☐ NO
Absent blood pressure by non-invasive monitoring	☐ YES	☐ NO
Flat arterial line tracing	☐ YES	☐ NO
Pulseless electrical activity (non perfusing rhythm)	☐ YES	☐ NO
Flat electrocardiogram tracing (standard 3 lead ECG)	☐ YES	☐ NO
Absent breath sounds by auscultation	☐ YES	☐ NO
Absent pulse oximetry (no oxygen saturation and/or no plethysmography tracing)	☐ YES	☐ NO
Unresponsiveness to painful stimulus	☐ YES	☐ NO
Fixed and dilated pupils	☐ YES	☐ NO
Other Specify:_____	☐ YES	☐ NO

D. If you use a specific time of observation of diagnostic tests or a "no touch time" as part of the process for declaring death, please indicate the time period waited and any other pertinent details:

Time of observation of diagnostic tests or "no-touch" time: _____

Comments:

_____

_____

13. DECLARATION OF DEATH (CONTINUED)

E. What other measures, if any, do you use to confirm the determination of death after cardiac arrest (Please check your responses in the table below)

Repeat your diagnostic tests	☐ YES	☐ NO
Get confirmation by a second physician	☐ YES	☐ NO
Other Specify:_____	☐ YES	☐ NO

F. If the diagnostic tests were repeated how many minutes after completing your tests the first time, did you repeat the evaluation?

Please indicate the number or "NA" if not applicable in the box ☐

CRF Completion Instructions:
Section 14. "Return of Circulation (Autoresuscitation)"

For the purposes of this study, autoresuscitation is defined as an unassisted return of spontaneous circulation (ROSC) after a declaration of death. ROSC is defined as one or more of the following signs: heart sounds by auscultation, pulse (detected by palpation or doppler), blood pressure (detected by invasive or non-invasive methods), oxygenation (detected by pulse oximetry), and resumption of breathing or other neurologic function (detected by EEG or clinical observation).

Did autoresuscitation occur: Indicate if autoresuscitation (as defined above) occurred. If "Yes", please have the appropriate care team member fill in the remainder of the form.

If autoresuscitation did not occur, no further information is required for this form.

GENERAL CRF INSTRUCTIONS:

At the top of each page, enter your Centre number and the Subject's number.

- Enter dates in the format dd/mmm/yyyy (i.e. 22/OCT/2015)
- Enter times according to the 24 hour clock in the format HH:MM (i.e. 4pm is entered 16:00)
- If data is not applicable, not known, illegible, or incorrect, enter N/A. **There should be no blank spaces**

If you enter a value and realize that it is incorrect, please put a line through it, date and initial it and enter the correct value.

EXAMPLE: ~~1 5 0 . 0 0~~ 175.00 RW

***Once the paper form is complete, please enter it electronically at www.deppart.org**

14. RETURN OF CIRCULATION (AUTORESUSCITATION)

*****ORIGINAL FORM TO BE COMPLETED BY THE MOST RESPONSIBLE PHYSICIAN AT THE TIME OF DECLARATION OF DEATH*****

Autoresuscitation is defined as an unassisted return of spontaneous circulation (ROSC) after a declaration of death.

Did autoresuscitation occur? ☐ **YES** ☐ **NO** (*If no, continue to next page →)*

If YES:

	Time (hh:mm)	**Date** (dd/mmm/yyyy)
Time and date of occurrence of autoresuscitation	|__|__|: |__|__|	|__|__| |__|__|__| | 2 | 0 | 1 |__|

Reported by:
☐ Physician ☐ Nurse ☐Other: Specify_____

Description of event:

_____
_____
_____
_____

Are medical personnel willing to be contacted by study investigators to describe the event further for witnessed cases of autoresuscitation?

☐YES ☐NO

Contact Information:

Name: _____
Email: _____

Contact Information:

Name: _____
Email: _____

Contact Information:

Name: _____
Email: _____

CRF Completion Instructions:
Section 15. "Protocol Deviations & Violations"

Record if there were any protocol deviations or violations for this patient.

If there were No protocol deviations, or violations do not complete any further information on this page.

Record all protocol deviations and violations and give reasons for their occurrence.

Protocol deviation: *any minor changes to the protocol or study procedures that occurred during this enrollment (e.g. incomplete forms, loss of data, issues with waveform signals, unable to capture 15 minutes of recording prior to WLST or 30 minutes after declaration of death, etc.)*

Protocol violation: *major changes involving inclusion/exclusion criteria or issues that result (or could have resulted) in subject withdrawal or improper recruitment (e.g. enrolled patient who met or later met exclusion criteria, enrolled but did not obtain consent, etc.).* ***Please notify coordinating center of any protocol violations immediately****.*

GENERAL CRF INSTRUCTIONS:

At the top of each page, enter your Centre number and the Subject's number.

- Enter dates in the format dd/mmm/yyyy (i.e. 22/OCT/2015)
- Enter times according to the 24 hour clock in the format HH:MM (i.e. 4pm is entered 16:00)
- If data is not applicable, not known, illegible, or incorrect, enter N/A. **There should be no blank spaces**

If you enter a value and realize that it is incorrect, please put a line through it, date and initial it and enter the correct value.

EXAMPLE: ~~1 5 0 . 0 0~~ 175.00 RW

***Once the paper form is complete, please enter it electronically at www.deppart.org**

15. PROTOCOL DEVIATIONS & VIOLATIONS

15.1 Were there any protocol deviations or violations?

☐YES ☐NO *(If no, continue to next page →)*

15.2 Please describe any protocol deviations that occurred:

☐ **Monitor(s) removed prior to declaration of death**

Reason:_____

_____

☐ **Problems with ECG, O2 saturation or arterial line**

Reason:_____

_____

☐ **Loss of waveform data during transfer to central monitor**

Reason:_____

_____

☐ **Other (specify)**

Reason:_____

_____

15.3 Please describe any protocol violations (patient data not useable for study) that occurred:

☐ **Did not meet inclusion/exclusion criteria**

Reasons for non-compliance to the protocol:_____

_____

☐ **Subject withdrawn because of family or healthcare team**

Reason:_____

_____

Did the family give permission for collected data to be used in analysis? ☐YES ☐NO

☐ **Other (specify)**

Reason:_____

_____

CRF Completion Instructions:
Section 16. "Variables to be Collected by Remote Monitoring System"

Please indicate which monitors were in place during WLST. Note that the 3-lead ECG, invasive blood pressure monitoring, and pulse oximeter and plethysmography monitoring must be in place for the patient to be enrolled in the DePPaRT study.

Record whether any of the monitors were removed prior to the declaration of death and if so, indicate the reason for their removal.

Removal of monitors (ECG, ART, or PLETH) should also be included in Section 18 as a protocol deviation.

GENERAL CRF INSTRUCTIONS:

At the top of each page, enter your Centre number and the Subject's number.

- Enter dates in the format dd/mmm/yyyy (i.e. 22/OCT/2015)
- Enter times according to the 24 hour clock in the format HH:MM (i.e. 4pm is entered 16:00)
- If data is not applicable, not known, illegible, or incorrect, enter N/A. **There should be no blank spaces**

If you enter a value and realize that it is incorrect, please put a line through it, date and initial it and enter the correct value.

EXAMPLE: ~~1 5 0 . 0 0~~ 175.00 RW

***Once the paper form is complete, please enter it electronically at www.deppart.org**

16. VARIABLES TO BE COLLECTED BY REMOTE MONITORING SYSTEM

Monitoring Systems in place:

Monitors in place at time of WLST. If removed, please explain why:

a) **3-lead Electrocardiogram (ECG)** ☐ Yes
Monitor removed prior to declaration of death? ☐ Yes ☐ No
If yes why removed: _____

b) **Invasive Arterial Blood Pressure** ☐ Yes
Monitor removed prior to declaration of death? ☐ Yes ☐ No
If yes why removed: _____

c) **Pulse oximeter and plethysmography** ☐ Yes
Monitor removed prior to declaration of death? ☐ Yes ☐ No
If yes why removed: _____

d) **Electroencephalogram** ☐ Yes ☐ No
Monitor removed prior to declaration of death? ☐ Yes ☐ No ☐ NA
If yes why removed: _____

e) **End-Tidal Carbon Dioxide** ☐ Yes ☐ No
Monitor removed prior to declaration of death? ☐ Yes ☐ No ☐ NA
If yes why removed: _____

CRF Completion Instructions:
Section 17. "General Comments"

Please provide any comments that you would like to add regarding the study procedures as it relates to this enrolled patient. Items that you may wish to comment on:

- Comments regarding the consent process: Did it go smoothly?
- Comments regarding the study procedures at the bedside: How do you think that the bedside team felt about the study? Were there any technical difficulties that arose?
- Comments regarding any concern about the family's interaction with the patient as a result of the study procedures.
- Or any other comments that you would like to make.

The above are suggestions only – you do not have to make any comment if you do not wish to do so. Comments will remain confidential.

GENERAL CRF INSTRUCTIONS:

At the top of each page, enter your Centre number and the Subject's number.

- Enter dates in the format dd/mmm/yyyy (i.e. 22/OCT/2015)
- Enter times according to the 24 hour clock in the format HH:MM (i.e. 4pm is entered 16:00)
- If data is not applicable, not known, illegible, or incorrect, enter N/A. **There should be no blank spaces**

If you enter a value and realize that it is incorrect, please put a line through it, date and initial it and enter the correct value.
EXAMPLE: ~~1 5 0 . 0 0~~ 175.00 RW

***Once the paper form is complete, please enter it electronically at www.deppart.org**

17. GENERAL COMMENTS

No, I do not wish to add any comments. ☐

CRF Completion Instructions:
Section 18. "Sign-Off Sheet"

The Research Assistant and Site Investigator must sign and date to confirm that the Case Report Form is complete and accurate to the best of their knowledge.

Please transfer all information from the paper CRF to the website. Keep a copy of the CRF with the patient's study files in a secure location as per your institution's policy.

GENERAL CRF INSTRUCTIONS:

At the top of each page, enter your Centre number and the Subject's number.

- Enter dates in the format dd/mmm/yyyy (i.e. 22/OCT/2015)
- Enter times according to the 24 hour clock in the format HH:MM (i.e. 4pm is entered 16:00)
- If data is not applicable, not known, illegible, or incorrect, enter N/A. **There should be no blank spaces**

If you enter a value and realize that it is incorrect, please put a line through it, date and initial it and enter the correct value.
EXAMPLE: ~~1 5 0 . 0 0~~ 175.00 RW

***Once the paper form is complete, please enter it electronically at www.deppart.org**

18. SIGN-OFF SHEET

Case Report Form to be signed off when the data has been checked as accurate and complete.

Research Assistant: _____ **Date:** _____

Site Investigator: _____ **Date:** _____

A COPY OF THIS CASE REPORT FORM SHOULD BE KEPT IN FILE AT YOUR INSTITUTION WITH THE PATIENT'S STUDY FILES.