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Title: The Neurologic Physiology after Removal of Therapy (NeuPaRT) study: A multicentre, prospective, observational, pilot feasibility study of neurophysiology after withdrawal of life-sustaining measures

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Roles and Responsibilities:

1. Protocol contributors:
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3. Role of Study Sponsor and funders:

a. Dr. Gofton is the study sponsor for this investigator-initiated study. Dr. Gofton is an associate scientist at the Lawson Health Research Institute. Together with the co-principal investigators listed above, Dr. Gofton completed study design and will be responsible for all study activities including data collection, management, analysis, interpretation of the results, writing of the final report and submission for publication.
b. The study is funded by the Canadian Institutes of Health Research, the Government of Canada New Frontiers in Research Fund and the Academic Medical Organisation of Southwestern Ontario. The study funders did not contribute to study design. The study funders will not be involved in data collection, management or analysis, interpretation of results, writing of the final report or the decision to submit the report for publication. They do not have authority over these activities.

4. Coordinating Centre: London Health Sciences Centre, University Hospital Site
5. Steering Committee:
    a. Members: Teneille Gofton (co-chair), Marat Slessarev (co-chair), Sonny Dhanani, Maureen Meade, Gord Boyd, Michael Chasse, Erika Chamberlain, Jennifer Chandler, Yun-Hee Choi, Frederick D'Aragon, Derek Debicki, Shane English, Tadeu Fantaneanu, Andreas Kramer, Julie Kromm, Loretta Norton, Nathan Scales, Jeff Singh, Maxwell Smith, Charles Weijer, Sam Shemie, Tracey Bentall, Eileen Campbell, Donor Family Partner: Laurie Blackstock

ABSTRACT

Introduction: In donation after circulatory determination of death, death is declared 5 minutes after circulatory arrest. This practice assumes, but does not explicitly confirm, permanent loss of brain activity. While this assumption is rooted a strong physiologic rationale, paucity of direct human data regarding temporal relationship between cessation of brain activity and circulatory arrest during the dying process threatens public and healthcare provider trust in deceased organ donation.

Methods and analysis: In this cohort study, we will prospectively record cerebral and brainstem electrical activity, cerebral blood flow velocity, and arterial blood pressure using electroencephalography (EEG), brainstem evoked potentials, transcranial doppler and bedside hemodynamic monitors in adult patients undergoing planned withdrawal of life sustaining measures in the intensive care units at 5 hospital sites for 18 months. We will use MATLAB to synchronize waveform data and compute the time of cessation of each signal relative to circulatory arrest. Our primary outcome is the feasibility of patient accrual, while secondary outcomes are 1) proportion of patients with complete waveform recordings and data transfer to coordinating site, and 2) time difference between cessation of neurophysiologic signals and circulatory arrest. We expect to to accrue 1 patient/site/month for a total of 90 patients.

Ethics and dissemination: We have ethics approval from Clinical Trials Ontario (Protocol #3862) and the relevant Research Ethics Board for each site. We will obtain written informed consent from legal substitute decision makers. We will present study results at research conferences including donor family partner forum and in peer-reviewed publications.

Registration: clinicaltrials.gov identifier NCT05306327

KEY WORDS

Death

Electroencephalography

Evoked potentials

Tissue and Organ Procurement

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This protocol will assess the feasibility of multicentre recording of cortical activity, brain blood flow velocity, and brainstem electrical activity in dying patients to inform deceased organ donation practices.
- Novel prospective multimodal measurement of brain activity and blood flow in a unique patient population and context.
- The multicentered prospective study design will provide generalizable data with external validity.
- The study will not impact withdrawal of life sustaining measures, dying or organ donation processes.
- Study results will serve as a surrogate for consciousness but cannot provide specific insight into the presence or absence of consciousness.

INTRODUCTION

Current organ donation after circulatory determination of death (DCDD) processes *assume, but do not explicitly confirm*, permanent loss of brain activity when death is determined 5 minutes after circulatory arrest. While this assumption is rooted in a strong physiologic rationale, a lack of neurophysiologic evidence regarding cessation of brain activity in humans contributes to ethical concerns[1] and ongoing mistrust of the DCDD process among healthcare and public stakeholders[2-4]. Healthcare providers may have uncertainty that waiting 5 minutes after circulatory arrest is sufficient to declare death in DCDD and ensure a permanent cessation of all brain activity prior to organ retrieval.[2-5]Furthermore, ensuring protection from suffering is critical to maintaining trust among donor families, healthcare providers and the public. Rigorous scientific evidence to determine when brain activity stops relative to circulatory arrest will help to confirm the safety of existing procedures and promote trust in the DCDD process.

A recent international multi-center study confirmed that waiting 5 minutes after circulatory arrest before death determination is sufficient to ensure permanence of cessation of systemic circulation[6]. Cessation of circulation is necessary to confirm death prior to organ retrieval. The cessation of circulation implies absence of brain function. However, it is not known if this time is sufficient to ensure permanent cessation of brain activity and to avoid donor harm. By objectively confirming when brain activity stops relative to circulatory arrest after withdrawal of life sustaining measures (WLSM), our study will help inform the appropriate duration for the observation period prior to determination of circulatory death in deceased organ donation that will avoid donor harm and optimise the quality of donated organs.

The temporal relationship between cessation of brain function and circulatory arrest may be affected by several patient- and practice-level factors. Approaches to the WLSM may affect cessation of circulation and brain activity and these practices are known to vary among institutions and geographical regions[7 8]. For example, at some centres patients are extubated, while at other centres they remain intubated despite the withdrawal of other life sustaining measures. Early extubation results in earlier hypoxia, which may accelerate cessation of brain activity relative to circulatory arrest. Furthermore, variation in the etiology of critical illness among different intensive care units (e.g., neurologic vs trauma vs cardiovascular units) may affect the dying process after WLSM. Thus, the time to arrest of brain activity may vary among institutions. Multicentre research is needed to ensure a representative cross-section of practice and enhance external validity of research investigating cessation of brain electrical activity.

In preparation for a large multicentre study, we will conduct a pilot multicentre feasibility trial to assess the feasibility of recording neurophysiologic data in adult patients during the dying process after WLSM at multiple sites. Results of this study will inform the design and conduct of a future large multicenter trial that will elucidate the temporal relationship between cessation of cortical and brainstem activity, cerebral blood flow velocity and circulatory arrest after WLSM in the intensive care unit. By informing DCDD practice, results of a future large trial will promote stakeholder trust and ensure donor protection from harm.

METHODS AND ANALYSIS

Patient and Public Involvement

A donor family partner has been involved in this study from the time of application for funding of the multicentred study and continues to contribute study activities at steering committee meetings. The donor family partner will not be involved in study recruitment, but will be most involved in data interpretation and dissemination as well as choosing which information to share with the public and the optimal language and format.

Study Objectives

This is a multicentre prospective observational cohort feasibility study that will measure cortical and brainstem electrical activity, cerebral blood flow velocity, and arterial blood pressure in adult patients during the dying process after WLSM in the intensive care units. Our primary objective is to determine the feasibility of patient accrual for assessing cortical electrical activity and cerebral blood flow velocity measured using electroencephalography (EEG) and transcranial doppler (TCD) at each site and to identify challenges to patient accrual. Our secondary objectives are to determine: 1) proportion of patients with complete EEG, TCD and arterial pulse pressure waveform;, 2) proportion of patients with complete transfer of waveform data to the London Health Sciences Centre (LHSC) site, and challenges to transferring complete waveform data; 3) time difference between circulatory arrest and cessation of EEG and TCD signals; 4) estimate of arterial pulse pressure and blood oxygenation at the time of cessation of EEG and TCD signals; 5) accrual of patients who complete evoked potentials and event-related potentials (ERP) at LHSC site; 5) time difference between circulatory arrest and

cessation of somatosensory evoked potentials (SSEP), brainstem auditory evoked potentials (BAEP) and ERP signals.

Consent

Because participants are not expected to have capacity, written informed consent will be obtained from the legally authorized substitute decision maker/surrogate for the participant. Building on our experience from the DePPart study[9], the research team will obtain consent only after the clinical healthcare team and surrogate have reached a consensual decision for WLSM. After meeting with the organ donation organization, the clinical team will seek permission from the surrogate to be approached about a research study. Supports will be provided to the surrogate as required (e.g. palliative care medicine, social work, chaplaincy) and the informed consent process will not continue if it causes additional distress for the surrogate as stated by the surrogate or perceived by the research team. Informed written consent will be obtained by the research team prior to initiation of study procedures.

Participants

This study will enroll patients from the intensive care units at five participating academic centers (LHSC, Foothills Medical Centre in Calgary, the Ottawa Hospital, Kingston Health Sciences Centre, and the Centre Hospitalier de l'Université de Montréal). We will approach the substitute decision maker of consecutive patients who are ≥ 18 years, have a consensual plan for WLSM in the intensive care unit, have an indwelling arterial cannula for monitoring arterial pulse pressure, and the attending physicians anticipate death within 24 hours of WLSM.

Patients fulfilling criteria for death by neurologic criteria or with injuries that anatomically preclude neuromonitoring will be excluded.

Study Interventions

Continuous Video-Electroencephalography: EEG will be recorded (10-20 International System, Natus Neuroworks, Oakville, Canada) using the American Clinical Neurophysiology Society guidelines for EEG in suspected cerebral death[10]. Electrode impedances will be maintained within 100-10,000 Ohms. Interelectrode distances will be 10 cm. Digital tracings will be read by two certified electroencephalographers at LHSC, blinded to clinical and demographic patient characteristics, at a sensitivity of 2 uV/mm[10]. To mitigate artifacts, we will use a non-cephalic channel and standard video monitoring to exclude sources of artifact in the environment. The video component of the EEG will focus on the participants' bed and will not include other aspects of the room. Video-EEG is standard of care in critical care EEG[11].

Cerebral Blood Flow: Cerebral blood flow will be monitored using a standard TCD to record flow velocity bilaterally in the middle cerebral arteries. We will use 2-MHz pulsed probe to identify middle cerebral arteries[12]. After locating flow, we will secure doppler probes in place with a head harness, which will enable researchers to leave the room and provide the family with privacy. While insonation of carotid and vertebral arteries would enable more complete assessment of brain blood flow, it would require operator presence and changing patient's head position throughout the dying process, which would intrude on patient and family privacy.

Furthermore, the intermittent nature of these measurements would preclude temporal correlation with EEG.

Hemodynamic Monitoring: We will use standard hemodynamic monitors to record arterial pulse pressure using an existing indwelling arterial catheter, electrocardiography (ECG), and arterial oxygen saturation (SpO2) from plethysmography pulse oximeter. Data from hemodynamic monitors will be captured from bedside monitors. While bedside monitors differ between sites, we will collate data from different sites/monitors as previously reported[6].

Event-Related, Somatosensory and Brainstem Auditory Evoked Potentials: Event-related and evoked potentials will be performed in 18 patients at LHSC only. These patients will be enrolled in addition to the cohort of patients undergoing EEG and TCD at LHSC.

Standard evoked potential paradigms will follow the American Clinical Neurophysiological Society guidelines for auditory evoked potentials[13] or short-latency SSEP[14]. Briefly, evoked potentials involve the presentation of discrete stimuli (auditory or somatosensory) that repeat at prescribed intervals. We will present a series of repetitive, brief (100-300 µsec) auditory or somatosensory stimuli. Auditory stimuli will consist of either clicks or beeps presented into one ear only. Electrodes will be placed on scalp vertex (Cz according to the 10-20 EEG placement system) and at earlobes (A1/2) and will be able to record resultant electrical responses of the entire auditory pathways known to occur within 10ms from source generators in the brainstem and as late as 300ms in higher-order cortical processing areas after stimulus presentation in

healthy participants. Somatosensory stimuli will involve electrical median nerve stimulation at the wrist crease unilaterally. The stimulation produces visible abduction of the thumb. Electrodes placed on the scalp at CP3/4 (over primary somatosensory cortical areas) will record the electrical responses of the primary somatosensory system within 20-35ms after stimuli presentation.

Study protocol

See Figure 1 for a schematic representation of study procedures. The research team will apply neuromonitors (EEG, TCD, ERP, SSEP, or BAEP) prior to WLSM, start recording, and leave the room to provide the family with privacy. In our experience this set up takes approximately 30 minutes. For any given patient we will not use more than two neuromonitors (e.g. EEG plus TCD). Each neuromonitor will be applied by a trained research technician. First, we will apply EEG and/or ERP/EP electrodes using standard clinical procedures. We will then use TCD probes to identify middle cerebral arteries. When the appropriate signal is identified the probes will be fixed and held in place for the duration of the monitoring period using the provided head harness. Where feasible, the research team will take advantage of clinically indicated monitoring already in place at the time of study enrollment.

Once neuromonitors are applied, technicians will exit the room and the research team will initiate recordings and collect at least 10 minutes of baseline data prior to WLSM. There will be no restrictions on families' presence at the bedside as a result of the patient's participation in the study. The research team will not participate in any other aspect of end-of-life care, which

will be overseen by the primary care team. The family or health care team will be able to stop study procedures at any point during end of life care if they no longer wish to participate.

The clinical team will withdraw life sustaining measures in accordance with national guidelines[15] and standard hospital protocols. As per standard clinical practice, the bedside nurse may place bedside monitors in comfort mode to silence alarms; and they will ensure that the full range of possibilities, including the very lowest values, will be visible on the screen. This study is observational and to prevent changes to the standard of care as a result of neuromonitoring data, families and critical care staff will be blinded to neuromonitoring data by turning away / shielding neuromonitors screens from clinical staff.

Data recording will continue for 30 minutes following circulatory arrest (Figure 1) to ensure that we capture permanent cessation of all signals or will stop at 6 hours after initiation of WLSM. For DCDD donors, recording will stop 5 minutes after circulatory arrest to enable procedures for organ retrieval surgery. If any monitoring equipment (i.e., ECG leads, TCD probes) is detached at the request of staff or surrogates or for the purpose of organ donation, the subject will not be excluded from analysis; we will analyse data up to that point in time and consider this in relation to study feasibility. To enable synchronization of neurologic and hemodynamic data during data analysis, the clocks on neurologic monitors will be synchronized with the hemodynamic monitor clock.

Clinical Data Collection

Participant demographics, admission diagnosis and clinical information will be collected to assess baseline characteristics of the study group. Clinical information will include age, sex, height, weight, admission to critical care diagnosis, Acute Physiology and Chronic Health Evaluation (APACHE) II score, Glasgow Coma Scale (GCS), organ donation assessment by local organ donation organization, type of neuromonitors used, type/level of invasive/non-invasive mechanical ventilation (if applicable), if patient was receiving renal replacement therapy, mechanical circulatory support, and arterial/venous blood gas, serum lactate, in the 24hrs prior to WLSM. We will also record sedation score in the 12 hour period prior to WLSM (e.g Richmond Agitation-Sedation Scale). Some of these covariates will be used in the exploratory analysis to determine if they affect the temporal relationship between cessation of brain activity and circulatory arrest.

In addition to recording hemodynamic and neurological waveform data, we will record the following clinical variables during WLSM and for 30 minutes following circulatory arrest: hourly cumulative dose of sedative, analgesic, anxiolytic, or neuromuscular blocker agents before and after WLSM; hourly cumulative dose of vasopressors and inotropes; time of removal of life-sustaining measures (non-invasive/invasive ventilation, renal replacement therapy, mechanical circulatory support); and details regarding the clinical determination of death (date, time and who determined death).

Data Management and Validation

All waveform data will be acquired from bedside monitors at each study site. They will be transferred to the LHSC site via secure file transfer. We will verify the completeness of all waveforms for required elements including duration of recording, inclusion of baseline recording, circulatory arrest and recording for 30 minutes following determination of death (5 minutes in DCDD), and electrocardiogram recording required for waveform synchronisation. Waveforms will be adjudicated by two qualified physicians, with a third adjudicator if disagreement arises.

Sample Size

To assess patient accrual, our primary feasibility outcome, we plan to recruit patients for a period of 18 months across 5 sites. We expect to enroll 1 patient/site/month for a total of 90 patients over 18 months. This is based on recruitment achieved during pilot work[16]. If we enroll <9 patients/site after 18 months, we will conclude that the larger study will not be feasible and the study approach will need to be re-evaluated. At LHSC site, we will plan to enroll an additional 1 patient/month for 18 months (total 18 patients) for EP, SSEP and BAEP studies given the unique technical abilities at this site. Similar enrolment rates were achieved in a single-centre pilot study[16].To understand feasibility challenges and modify the research plan for a larger study we will analyze study accrual, complete waveform data, and success of data transfer to LHSC as outcomes regardless of the number of patients enrolled.

Data Analysis

We will use descriptive statistics to summarize the feasibility outcomes. For categorical variables, frequencies and percentages will be tabulated. For continuous variables, means, medians, standard deviations, interquartile ranges, maximum, and minimum will be tabulated. We will use MATLAB to synchronize and process waveform data, and SPSS to compute summary statistics. We will analyze each outcome as follows:

Patient Accrual: We will compute the proportion of patients who were eligible for enrollment, were enrolled, and completed full study protocol. We will identify those not enrolled due to lack of research coordinators, EEG/TCD/SSEP/BAEP/ERP technicians, or equipment. Accrual will be assessed on a per site basis.

Waveform Data: We will report the number of patients who have complete EEG/TCD/ERP/SSEP/BAEP and arterial pulse pressure data. We will summarize the reasons for all missing or incomplete EEG/TCD/ERP/SSEP/BAEP and arterial pulse pressure data (e.g., technician or equipment unavailable; equipment malfunction; other technical challenges, time of WLSM).

Waveform Data Transfer: We will report the number of patients from non-LHSC sites who successfully transfer all EEG, TCD and arterial pulse pressure data to LHSC. Successful data transfer will be defined as complete set of data files that is transferred and can be successfully opened for analysis at LHSC.

Time difference between circulatory arrest and cessation of brain activity: In each patient, we will use synchronized waveform data and MATLAB to plot and record the time of first cessation of EEG/TCD/ERP/SSEP/BAEP and arterial pulse pressure signals. We will then calculate the time difference between circulatory arrest and cessation of EEG/TCD/ERP/SSEP/BAEP signals. Both qualitative (visual inspection of raw EEG) and quantitative (coherence analysis) EEG analyses will be performed[16]. We will pool data across patients to calculate the mean and standard deviation for the sample across patients. Given the difference in patient mix and approaches to WLSM between sites, we will stratify our analysis by site.

Cessation of each waveform signal will be defined as follows:

1) *EEG Signal* - Defined based on the American Clinical Neurophysiology Society Guidelines for electrocerebral inactivity as identified by no EEG activity over 2 μV, without resumption of amplitude over 2 μV, when recording from electrode pairs 10 or more cm apart[10]. The exact time of electrocerebral inactivity will begin at the onset of <2 μV for at least 60 seconds and will be determined by visual inspection by two adjudicators who are qualified electroencephalographers and will begin.
2) *TCD Signal* - Defined based on previously published definitions as the appearance of Doppler spectra suggesting biphasic oscillating flow or small systolic spikes of <200 ms duration and <50 cm/s pulse systolic velocity spike[17]. The exact time of cessation of cerebral blood flow will begin at the onset of when these criteria are met for at least 60 seconds and will be determined by two adjudicators qualified in ultrasonography.

3) *Arterial pulse pressure (i.e. circulatory arrest)* - Defined as a pulse pressure of ≤5 mmHg that persists for at least 60 seconds[6]. The exact timing of cessation of arterial pulse pressure will be determined by two blinded adjudicators. Discrepancies will be resolved by consensus by a panel of experts in neurocritical care.

4) *Evoked potentials and event-related potentials* – Cessation of brainstem function will be defined as timing of the loss of wave V, indicating loss of function within the rostral pons. Cessation of cortical function may be defined as the time of cessation of a 40Hz auditory steady state response which is a type of event-related potential that is generated in the primary auditory cortex in the supratemporal plane. The time of loss of wave V will begin at the onset of when these criteria are met for at least 60 seconds and will be determined by two adjudicators.

Data Analysis Plan

For categorical variables, frequencies and percentages will be tabulated. For continuous variables, means, medians, standard deviations, interquartile ranges, maximum, and minimum will be tabulated. We will use MATLAB to synchronize and process waveform data, and SPSS to compute summary statistics.

We will analyze each outcome as follows:

1. *Patient accrual:* We will compute proportion of patients who were 1) eligible for enrollment, 2) were enrolled, 3) complete full study protocol, 4) were not enrolled due

to lack of research coordinators, EEG/TCD/event-related/SSEP/BAEP technicians, or equipment. A minimum of 80% patients will be required to have a complete dataset.

2. *Complete waveform data:* We will compute the number of patients who have complete EEG/TCD/ERP/SSEP/BAEP and arterial pulse pressure signals. A complete dataset for each signal will be defined as an adequate waveform signal that (i) spans circulatory arrest, (ii) includes data for at least 80% of the planned observation period and (iii) has a clearly identifiable time of cessation for each signal (as defined, below).
3. *Waveform data transfer to LHSC:* We will compute the number of patients from non-LHSC sites who have successful transfer of all EEG, TCD and ABP data to LHSC. A minimum of 80% successful data transfers will be required.
4. *Time difference between circulatory arrest and cessation of brain activity:* In each patient, we will use synchronized waveform data and MATLAB to plot and record the time of first cessation of EEG/TCD/EP/SSEP/BAEP and ABP signals. We will then calculate the time difference between circulatory arrest and cessation of EEG/TCD/EP/SSEP/BAEP signals. We will pool data across patients to calculate whether data fits a normal distribution and the mean/median and standard deviation/interquartile range/confidence interval for the sample across patients. Given the difference in patient mix and approaches to WLSM between sites, we will report patient characteristics and cause of death by site and compute the differences between sites. We will test if the average time differences between sites are different. Data from all sites will be pooled and a meta-analysis will be performed to synthesize the average time differences across sites. We will perform a regression analysis to examine whether factors such as cause of

death, approach to WLSM, age, sex, and medication exposure influence the time difference.

5. *Cessation of each brain activity signal* will be defined as outlined in previous sections.

ETHICS AND DISSEMINATION

The study will be conducted in accordance with the ethical requirements outlined in the Tri-Council Policy Statement on the Ethical Conduct for research involving Humans and all relevant national and local guidelines on the ethical conduct of research. The protocol for this project has been approved by Clinical Trials Ontario (Protocol #3862) and the relevant Health Sciences Research Ethics Boards for each participating site. Full study approval is currently in place at LHSC and other study site applications are under review by the local ethics committees. Informed consent will be obtained from patients with capacity to consent prior to enrollment or from the legally authorized substitute decision maker for patients lacking capacity. Elsewhere we have published a detailed ethical analysis of this study's protocol[9].

Review of ongoing study activities will occur every three months by the steering committee, which includes the donor family partner, and updates on study progress will be presented to Canadian Critical Care Trials Group and the Canadian Donation and Transplantation Research Program. Study newsletters will update stakeholders throughout the conduct of the study. Dissemination of study results will occur through presentation at scientific meetings, communication with relevant organ donation organizations, local hospital staff and relevant patient advocacy organizations and at donor family/patient forums.

DISCUSSION

Current DCDD practice assumes, but does not explicitly confirm, permanent loss of brain activity when death is declared 5 minutes after circulatory arrest. Establishing when brain activity stops relative to circulatory arrest in patients undergoing planned WLSM will inform DCDD practice, promote stakeholder trust and ensure donor protection from harm. Establishing this evidence will require a larger multicentre observational trial to confirm external validity and inform clinical practice. Given that this is a new area of research associated with logistical, technical and ethical challenges, this multicentre pilot study is essential to establish the feasibility, identify potential challenges and collect pilot data to inform the larger study.

The results from this study will be able to provide direct objective evidence for the timing for cessation of cortical electrical activity (EEG), loss of brainstem auditory pathway transmission to the cortex (ERP), brainstem auditory pathway electrical activity (BAEP/SSEP) and cessation of forward blood flow in the middle cerebral arteries (TCD). The results will not, however, be able to provide definitive data about the presence or absence of consciousness, whole brain function, interneuronal communication and neuronal function at the cellular level or whole brain perfusion. Consciousness, whole brain function, neuronal function at the cellular level and whole brain perfusion would be very challenging to measure non-invasively and in a manner that respects patient and family privacy at a very difficult time of life. Despite these limitations, this study will provide rich feasibility data in addition to data of interest to neuroscientists, critical care, palliative care and organ donation communities, ethicists, legal scholars, and policy experts. Our pilot multicentre feasibility trial will help inform design and conduct of this larger

study, and will provide the first moderately sized prospective multicentre study in humans that will shed light on the neurobiology of the dying process.

FIGURE LEGEND

Figure 1. Timeline outlining study procedures. Abbreviations: BAEP = brainstem auditory evoked potentials; EEG = continuous video-electroencephalography; EP = event-related potentials; SSEP = somatosensory evoked potential; TCD = transcranial doppler; WLSM = withdrawal of life sustaining measures

CONTRIBUTORS

TEG, MS, MM, SD, LN and DD contributed to the conception of the work within this manuscript, development of the final protocol, drafting and revising of the manuscript and final approval of the version to be submitted. GB, EC, JC, MC, NBS, YHC, FDA, SWE, TAF, AK, JK, VK, NBM, JMS, MJS, CW, SS, TB and EC all contributed to revising the manuscript and final approval of the version to be submitted.

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TEG has received an honorarium from Novartis and research funding from the Academic Medical Organisation of Southwestern Ontario and Lawson Health Research Institute Internal Research Fund for unrelated research. SWE is supported by a Heart and Stroke Foundation National New Investigator Award. FDA is supported by the Fond de recherche du Québec-Santé career Award. CW receives consulting income from Cardialen, Eli Lilly & Company, and Research Triangle Institute International. GB, EC, JC, MC, NBS, YHC, TAF, AK, JK, VK, NBM, JMS and MJS declare no competing interests. MS receives a stipend for his work as a Regional Medical Lead (Donation) with Ontario Health (Trillium Gift of Life Network).

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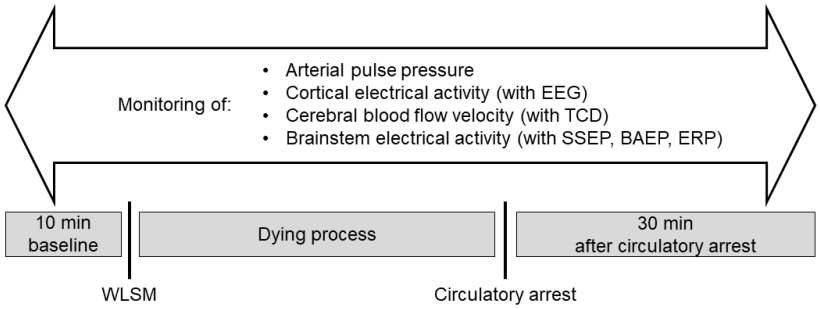

Figure 1. Timeline outlining study procedures. Abbreviations: BAEP = brainstem auditory evoked potentials; EEG = continuous video-electroencephalography; EP = event-related potentials; SSEP = somatosensory evoked potential; TCD = transcranial doppler; WLSM = withdrawal of life sustaining measures

338x190mm (96 x 96 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1, 4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7-8
Objectives	3	State specific objectives, including any prespecified hypotheses	8, 9
Methods			
Study design	4	Present key elements of study design early in the paper	9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	10-11
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	15, 17, 18
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	19
Bias	9	Describe any efforts to address potential sources of bias	Multi-centre
Study size	10	Explain how the study size was arrived at	16
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	15
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	17-21
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	Report numbers of outcome events or summary measures over time	N/A

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	N/A
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	22
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	N/A
Generalisability	21	Discuss the generalisability (external validity) of the study results	6
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

The Neurologic Physiology after Removal of Therapy (NeuPaRT) study: Study protocol of a multicentre, prospective, observational, pilot feasibility study of neurophysiology after withdrawal of life-sustaining measures

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Primary Subject	Intensive care

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ABSTRACT

Introduction: In donation after circulatory determination of death, death is declared 5 minutes after circulatory arrest. This practice assumes, but does not explicitly confirm, permanent loss of brain activity. While this assumption is rooted a strong physiologic rationale, paucity of direct human data regarding temporal relationship between cessation of brain activity and circulatory arrest during the dying process threatens public and healthcare provider trust in deceased organ donation.

Methods and analysis: In this cohort study, we will prospectively record cerebral and brainstem electrical activity, cerebral blood flow velocity, and arterial blood pressure using electroencephalography (EEG), brainstem evoked potentials, transcranial doppler and bedside hemodynamic monitors in adult patients undergoing planned withdrawal of life sustaining measures in the intensive care units at 5 hospital sites for 18 months. We will use MATLAB to synchronize waveform data and compute the time of cessation of each signal relative to circulatory arrest. Our primary outcome is the feasibility of patient accrual, while secondary outcomes are 1) proportion of patients with complete waveform recordings and data transfer to coordinating site, and 2) time difference between cessation of neurophysiologic signals and circulatory arrest. We expect to to accrue 1 patient/site/month for a total of 90 patients.

Ethics and dissemination: We have ethics approval from Clinical Trials Ontario (Protocol #3862) and the relevant Research Ethics Board for each site. We will obtain written informed consent from legal substitute decision makers. We will present study results at research conferences including donor family partner forum and in peer-reviewed publications.

Registration: clinicaltrials.gov identifier NCT05306327

KEY WORDS

Death

Electroencephalography

Evoked potentials

Tissue and Organ Procurement

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This protocol will assess the feasibility of multicentre recording of cortical activity, brain blood flow velocity, and brainstem electrical activity in dying patients to inform deceased organ donation practices.
- Novel prospective multimodal measurement of brain activity and blood flow in a unique patient population and context.
- The multicentered prospective study design will provide generalizable data with external validity.
- The study will not impact withdrawal of life sustaining measures, dying or organ donation processes.
- Study results will serve as a surrogate for consciousness but cannot provide specific insight into the presence or absence of consciousness.

INTRODUCTION

Current organ donation after circulatory determination of death (DCDD) processes *assume, but do not explicitly confirm*, permanent loss of brain activity when death is determined 5 minutes after circulatory arrest. While this assumption is rooted in a strong physiologic rationale, a lack of neurophysiologic evidence regarding cessation of brain activity in humans contributes to ethical concerns[1] and ongoing mistrust of the DCDD process among healthcare and public stakeholders[2-4]. Healthcare providers may have uncertainty that waiting 5 minutes after circulatory arrest is sufficient to declare death in DCDD and ensure a permanent cessation of all brain activity prior to organ retrieval.[2-5]Furthermore, ensuring protection from suffering is critical to maintaining trust among donor families, healthcare providers and the public. Rigorous scientific evidence to determine when brain activity stops relative to circulatory arrest will help to confirm the safety of existing procedures and promote trust in the DCDD process.

A recent international multi-center study confirmed that waiting 5 minutes after circulatory arrest before death determination is sufficient to ensure permanence of cessation of systemic circulation[6]. Cessation of circulation is necessary to confirm death prior to organ retrieval. The cessation of circulation implies absence of brain function. However, it is not known if this time is sufficient to ensure permanent cessation of brain activity and to avoid donor harm. By objectively confirming when brain activity stops relative to circulatory arrest after withdrawal of life sustaining measures (WLSM), our study will help inform the appropriate duration for the observation period prior to determination of circulatory death in deceased organ donation that will avoid donor harm and optimise the quality of donated organs.

The temporal relationship between cessation of brain function and circulatory arrest may be affected by several patient- and practice-level factors. Approaches to the WLSM may affect cessation of circulation and brain activity and these practices are known to vary among institutions and geographical regions[7 8]. For example, at some centres patients are extubated, while at other centres they remain intubated despite the withdrawal of other life sustaining measures. Early extubation results in earlier hypoxia, which may accelerate cessation of brain activity relative to circulatory arrest. Furthermore, variation in the etiology of critical illness among different intensive care units (e.g., neurologic vs trauma vs cardiovascular units) may affect the dying process after WLSM. Thus, the time to arrest of brain activity may vary among institutions. Multicentre research is needed to ensure a representative cross-section of practice and enhance external validity of research investigating cessation of brain electrical activity.

In preparation for a large multicentre study, we will conduct a pilot multicentre feasibility trial to assess the feasibility of recording neurophysiologic data in adult patients during the dying process after WLSM at multiple sites. Results of this study will inform the design and conduct of a future large multicenter trial that will elucidate the temporal relationship between cessation of cortical and brainstem activity, cerebral blood flow velocity and circulatory arrest after WLSM in the intensive care unit. By informing DCDD practice, results of a future large trial will promote stakeholder trust and ensure donor protection from harm.

METHODS AND ANALYSIS

Patient and Public Involvement

A donor family partner has been involved in this study from the time of application for funding of the multicentred study and continues to contribute study activities at steering committee meetings. The donor family partner will not be involved in study recruitment, but will be most involved in data interpretation and dissemination as well as choosing which information to share with the public and the optimal language and format.

Study Objectives

This is a multicentre prospective observational cohort feasibility study that will measure cortical and brainstem electrical activity, cerebral blood flow velocity, and arterial blood pressure in adult patients during the dying process after WLSM in the intensive care units. Our primary objective is to determine the feasibility of patient accrual for assessing cortical electrical activity and cerebral blood flow velocity measured using electroencephalography (EEG) and transcranial doppler (TCD) at each site and to identify challenges to patient accrual. Our secondary objectives are to determine: 1) proportion of patients with complete EEG, TCD and arterial pulse pressure waveform;, 2) proportion of patients with complete transfer of waveform data to the London Health Sciences Centre (LHSC) site, and challenges to transferring complete waveform data; 3) time difference between circulatory arrest and cessation of EEG and TCD signals; 4) estimate of arterial pulse pressure and blood oxygenation at the time of cessation of EEG and TCD signals; 5) accrual of patients who complete evoked potentials and event-related potentials (ERP) at LHSC site; 5) time difference between circulatory arrest and

cessation of somatosensory evoked potentials (SSEP), brainstem auditory evoked potentials (BAEP) and ERP signals.

Consent

Because participants are not expected to have capacity, written informed consent will be obtained from the legally authorized substitute decision maker/surrogate for the participant. Building on our experience from the DePPart study[9], the research team will obtain consent only after the clinical healthcare team and surrogate have reached a consensual decision for WLSM. After meeting with the organ donation organization, the clinical team will seek permission from the surrogate to be approached about a research study. Supports will be provided to the surrogate as required (e.g. palliative care medicine, social work, chaplaincy) and the informed consent process will not continue if it causes additional distress for the surrogate as stated by the surrogate or perceived by the research team. Informed written consent will be obtained by the research team prior to initiation of study procedures.

Participants

This study will enroll patients from the intensive care units at five participating academic centers (LHSC, Foothills Medical Centre in Calgary, the Ottawa Hospital, Kingston Health Sciences Centre, and the Centre Hospitalier de l'Université de Montréal) beginning in August 2022 for a duration of 3 years. We will approach the substitute decision maker of consecutive patients who are $\geq$ 18 years, have a consensual plan for WLSM in the intensive care unit, have an indwelling arterial cannula for monitoring arterial pulse pressure, and the attending

physicians anticipate death within 24 hours of WLSM. Patients fulfilling criteria for death by neurologic criteria or with injuries that anatomically preclude neuromonitoring will be excluded.

Study Interventions

Continuous Video-Electroencephalography: EEG will be recorded (10-20 International System, Natus Neuroworks, Oakville, Canada) using the American Clinical Neurophysiology Society guidelines for EEG in suspected cerebral death[10]. Electrode impedances will be maintained within 100-10,000 Ohms. Interelectrode distances will be 10 cm. Digital tracings will be read by two certified electroencephalographers at LHSC, blinded to clinical and demographic patient characteristics, at a sensitivity of 2 uV/mm[10]. To mitigate artifacts, we will use a non-cephalic channel and standard video monitoring to exclude sources of artifact in the environment. The video component of the EEG will focus on the participants' bed and will not include other aspects of the room. Video-EEG is standard of care in critical care EEG[11].

Cerebral Blood Flow: Cerebral blood flow will be monitored using a standard TCD to record flow velocity bilaterally in the middle cerebral arteries. We will use 2-MHz pulsed probe to identify middle cerebral arteries[12]. After locating flow, we will secure doppler probes in place with a head harness, which will enable researchers to leave the room and provide the family with privacy. While insonation of carotid and vertebral arteries would enable more complete assessment of brain blood flow, it would require operator presence and changing patient's head position throughout the dying process, which would intrude on patient and family privacy.

Furthermore, the intermittent nature of these measurements would preclude temporal correlation with EEG.

Hemodynamic Monitoring: We will use standard hemodynamic monitors to record arterial pulse pressure using an existing indwelling arterial catheter, electrocardiography (ECG), and arterial oxygen saturation (SpO2) from plethysmography pulse oximeter. Data from hemodynamic monitors will be captured from bedside monitors. While bedside monitors differ between sites, we will collate data from different sites/monitors as previously reported[6].

Event-Related, Somatosensory and Brainstem Auditory Evoked Potentials: Event-related and evoked potentials will be performed in 18 patients at LHSC only. These patients will be enrolled in addition to the cohort of patients undergoing EEG and TCD at LHSC.

Standard evoked potential paradigms will follow the American Clinical Neurophysiological Society guidelines for auditory evoked potentials[13] or short-latency SSEP[14]. Briefly, evoked potentials involve the presentation of discrete stimuli (auditory or somatosensory) that repeat at prescribed intervals. We will present a series of repetitive, brief (100-300 µsec) auditory or somatosensory stimuli. Auditory stimuli will consist of either clicks or beeps presented into one ear only. Electrodes will be placed on scalp vertex (Cz according to the 10-20 EEG placement system) and at earlobes (A1/2) and will be able to record resultant electrical responses of the entire auditory pathways known to occur within 10ms from source generators in the brainstem and as late as 300ms in higher-order cortical processing areas after stimulus presentation in

healthy participants. Somatosensory stimuli will involve electrical median nerve stimulation at the wrist crease unilaterally. The stimulation produces visible abduction of the thumb. Electrodes placed on the scalp at CP3/4 (over primary somatosensory cortical areas) will record the electrical responses of the primary somatosensory system within 20-35ms after stimuli presentation.

Study protocol

See Figure 1 for a schematic representation of study procedures. The research team will apply neuromonitors (EEG, TCD, ERP, SSEP, or BAEP) prior to WLSM, start recording, and leave the room to provide the family with privacy. In our experience this set up takes approximately 30 minutes. For any given patient we will not use more than two neuromonitors (e.g. EEG plus TCD). Each neuromonitor will be applied by a trained research technician. First, we will apply EEG and/or ERP/EP electrodes using standard clinical procedures. We will then use TCD probes to identify middle cerebral arteries. When the appropriate signal is identified the probes will be fixed and held in place for the duration of the monitoring period using the provided head harness. Where feasible, the research team will take advantage of clinically indicated monitoring already in place at the time of study enrollment.

Once neuromonitors are applied, technicians will exit the room and the research team will initiate recordings and collect at least 10 minutes of baseline data prior to WLSM. There will be no restrictions on families' presence at the bedside as a result of the patient's participation in the study. The research team will not participate in any other aspect of end-of-life care, which

will be overseen by the primary care team. The family or health care team will be able to stop study procedures at any point during end of life care if they no longer wish to participate.

The clinical team will withdraw life sustaining measures in accordance with national guidelines[15] and standard hospital protocols. As per standard clinical practice, the bedside nurse may place bedside monitors in comfort mode to silence alarms; and they will ensure that the full range of possibilities, including the very lowest values, will be visible on the screen. This study is observational and to prevent changes to the standard of care as a result of neuromonitoring data, families and critical care staff will be blinded to neuromonitoring data by turning away / shielding neuromonitors screens from clinical staff.

Data recording will continue for 30 minutes following circulatory arrest (Figure 1) to ensure that we capture permanent cessation of all signals or will stop at 6 hours after initiation of WLSM. For DCDD donors, recording will stop 5 minutes after circulatory arrest to enable procedures for organ retrieval surgery. If any monitoring equipment (i.e., ECG leads, TCD probes) is detached at the request of staff or surrogates or for the purpose of organ donation, the subject will not be excluded from analysis; we will analyse data up to that point in time and consider this in relation to study feasibility. To enable synchronization of neurologic and hemodynamic data during data analysis, the clocks on neurologic monitors will be synchronized with the hemodynamic monitor clock.

Clinical Data Collection

Participant demographics, admission diagnosis and clinical information will be collected to assess baseline characteristics of the study group. Clinical information will include age, sex, height, weight, admission to critical care diagnosis, Acute Physiology and Chronic Health Evaluation (APACHE) II score, Glasgow Coma Scale (GCS), organ donation assessment by local organ donation organization, type of neuromonitors used, type/level of invasive/non-invasive mechanical ventilation (if applicable), if patient was receiving renal replacement therapy, mechanical circulatory support, and arterial/venous blood gas, serum lactate, in the 24hrs prior to WLSM. We will also record sedation score in the 12 hour period prior to WLSM (e.g Richmond Agitation-Sedation Scale). Some of these covariates will be used in the exploratory analysis to determine if they affect the temporal relationship between cessation of brain activity and circulatory arrest.

In addition to recording hemodynamic and neurological waveform data, we will record the following clinical variables during WLSM and for 30 minutes following circulatory arrest: hourly cumulative dose of sedative, analgesic, anxiolytic, or neuromuscular blocker agents before and after WLSM; hourly cumulative dose of vasopressors and inotropes; time of removal of life-sustaining measures (non-invasive/invasive ventilation, renal replacement therapy, mechanical circulatory support); and details regarding the clinical determination of death (date, time and who determined death).

Data Management and Validation

All waveform data will be acquired from bedside monitors at each study site. They will be transferred to the LHSC site via secure file transfer. We will verify the completeness of all waveforms for required elements including duration of recording, inclusion of baseline recording, circulatory arrest and recording for 30 minutes following determination of death (5 minutes in DCDD), and electrocardiogram recording required for waveform synchronisation. Waveforms will be adjudicated by two qualified physicians, with a third adjudicator if disagreement arises.

Sample Size

To assess patient accrual, our primary feasibility outcome, we plan to recruit patients for a period of 18 months across 5 sites. We expect to enroll 1 patient/site/month for a total of 90 patients over 18 months. This is based on recruitment achieved during pilot work[16]. If we enroll <9 patients/site after 18 months, we will conclude that the larger study will not be feasible and the study approach will need to be re-evaluated. At LHSC site, we will plan to enroll an additional 1 patient/month for 18 months (total 18 patients) for EP, SSEP and BAEP studies given the unique technical abilities at this site. Similar enrolment rates were achieved in a single-centre pilot study[16].To understand feasibility challenges and modify the research plan for a larger study we will analyze study accrual, complete waveform data, and success of data transfer to LHSC as outcomes regardless of the number of patients enrolled.

Data Analysis

We will use descriptive statistics to summarize the feasibility outcomes. For categorical variables, frequencies and percentages will be tabulated. For continuous variables, means, medians, standard deviations, interquartile ranges, maximum, and minimum will be tabulated. We will use MATLAB to synchronize and process waveform data, and SPSS to compute summary statistics. We will analyze each outcome as follows:

Patient Accrual: We will compute the proportion of patients who were eligible for enrollment, were enrolled, and completed full study protocol. We will identify those not enrolled due to lack of research coordinators, EEG/TCD/SSEP/BAEP/ERP technicians, or equipment. Accrual will be assessed on a per site basis.

Waveform Data: We will report the number of patients who have complete EEG/TCD/ERP/SSEP/BAEP and arterial pulse pressure data. We will summarize the reasons for all missing or incomplete EEG/TCD/ERP/SSEP/BAEP and arterial pulse pressure data (e.g., technician or equipment unavailable; equipment malfunction; other technical challenges, time of WLSM).

Waveform Data Transfer: We will report the number of patients from non-LHSC sites who successfully transfer all EEG, TCD and arterial pulse pressure data to LHSC. Successful data transfer will be defined as complete set of data files that is transferred and can be successfully opened for analysis at LHSC.

Time difference between circulatory arrest and cessation of brain activity: In each patient, we will use synchronized waveform data and MATLAB to plot and record the time of first cessation of EEG/TCD/ERP/SSEP/BAEP and arterial pulse pressure signals. We will then calculate the time difference between circulatory arrest and cessation of EEG/TCD/ERP/SSEP/BAEP signals. Both qualitative (visual inspection of raw EEG) and quantitative (coherence analysis) EEG analyses will be performed[16]. We will pool data across patients to calculate the mean and standard deviation for the sample across patients. Given the difference in patient mix and approaches to WLSM between sites, we will stratify our analysis by site.

Cessation of each waveform signal will be defined as follows:

1) *EEG Signal* - Defined based on the American Clinical Neurophysiology Society Guidelines for electrocerebral inactivity as identified by no EEG activity over 2 µV, without resumption of amplitude over 2 µV, when recording from electrode pairs 10 or more cm apart[10]. The exact time of electrocerebral inactivity will begin at the onset of <2 µV for at least 60 seconds and will be determined by visual inspection by two adjudicators who are qualified electroencephalographers and will begin.
2) *TCD Signal* - Defined based on previously published definitions as the appearance of Doppler spectra suggesting biphasic oscillating flow or small systolic spikes of <200 ms duration and <50 cm/s pulse systolic velocity spike[17]. The exact time of cessation of cerebral blood flow will begin at the onset of when these criteria are met for at least 60 seconds and will be determined by two adjudicators qualified in ultrasonography.

3) *Arterial pulse pressure (i.e. circulatory arrest)* - Defined as a pulse pressure of ≤5 mmHg that persists for at least 60 seconds[6]. The exact timing of cessation of arterial pulse pressure will be determined by two blinded adjudicators. Discrepancies will be resolved by consensus by a panel of experts in neurocritical care.

4) *Evoked potentials and event-related potentials* – Cessation of brainstem function will be defined as timing of the loss of wave V, indicating loss of function within the rostral pons. Cessation of cortical function may be defined as the time of cessation of a 40Hz auditory steady state response which is a type of event-related potential that is generated in the primary auditory cortex in the supratemporal plane. The time of loss of wave V will begin at the onset of when these criteria are met for at least 60 seconds and will be determined by two adjudicators.

Data Analysis Plan

For categorical variables, frequencies and percentages will be tabulated. For continuous variables, means, medians, standard deviations, interquartile ranges, maximum, and minimum will be tabulated. We will use MATLAB to synchronize and process waveform data, and SPSS to compute summary statistics.

We will analyze each outcome as follows:

1. *Patient accrual:* We will compute proportion of patients who were 1) eligible for enrollment, 2) were enrolled, 3) complete full study protocol, 4) were not enrolled due

to lack of research coordinators, EEG/TCD/event-related/SSEP/BAEP technicians, or equipment. A minimum of 80% patients will be required to have a complete dataset.

2. *Complete waveform data:* We will compute the number of patients who have complete EEG/TCD/ERP/SSEP/BAEP and arterial pulse pressure signals. A complete dataset for each signal will be defined as an adequate waveform signal that (i) spans circulatory arrest, (ii) includes data for at least 80% of the planned observation period and (iii) has a clearly identifiable time of cessation for each signal (as defined, below).
3. *Waveform data transfer to LHSC:* We will compute the number of patients from non-LHSC sites who have successful transfer of all EEG, TCD and ABP data to LHSC. A minimum of 80% successful data transfers will be required.
4. *Time difference between circulatory arrest and cessation of brain activity:* In each patient, we will use synchronized waveform data and MATLAB to plot and record the time of first cessation of EEG/TCD/EP/SSEP/BAEP and ABP signals. We will then calculate the time difference between circulatory arrest and cessation of EEG/TCD/EP/SSEP/BAEP signals. We will pool data across patients to calculate whether data fits a normal distribution and the mean/median and standard deviation/interquartile range/confidence interval for the sample across patients. Given the difference in patient mix and approaches to WLSM between sites, we will report patient characteristics and cause of death by site and compute the differences between sites. We will test if the average time differences between sites are different. Data from all sites will be pooled and a meta-analysis will be performed to synthesize the average time differences across sites. We will perform a regression analysis to examine whether factors such as cause of

death, approach to WLSM, age, sex, and medication exposure influence the time difference.

5. *Cessation of each brain activity signal* will be defined as outlined in previous sections.

Requests for data sharing should be directed to the principal investigator (Dr. T. Gofton) and will be considered on a case by case basis and with approval from Clinical Trials Ontario and the Western Health Sciences Research Ethics Board. No video will be shared at any time.

ETHICS AND DISSEMINATION

The study will be conducted in accordance with the ethical requirements outlined in the Tri-Council Policy Statement on the Ethical Conduct for research involving Humans and all relevant national and local guidelines on the ethical conduct of research. The protocol for this project has been approved by Clinical Trials Ontario (Protocol #3862) and the relevant Health Sciences Research Ethics Boards for each participating site. Full study approval is currently in place at LHSC and other study site applications are under review by the local ethics committees. Informed consent will be obtained from patients with capacity to consent prior to enrollment or from the legally authorized substitute decision maker for patients lacking capacity. Elsewhere we have published a detailed ethical analysis of this study's protocol[9].

Review of ongoing study activities will occur every three months by the steering committee, which includes the donor family partner, and updates on study progress will be presented to Canadian Critical Care Trials Group and the Canadian Donation and Transplantation Research

Program. Study newsletters will update stakeholders throughout the conduct of the study. Dissemination of study results will occur through presentation at scientific meetings, communication with relevant organ donation organizations, local hospital staff and relevant patient advocacy organizations and at donor family/patient forums.

DISCUSSION

Current DCDD practice assumes, but does not explicitly confirm, permanent loss of brain activity when death is declared 5 minutes after circulatory arrest. Establishing when brain activity stops relative to circulatory arrest in patients undergoing planned WLSM will inform DCDD practice, promote stakeholder trust and ensure donor protection from harm. Establishing this evidence will require a larger multicentre observational trial to confirm external validity and inform clinical practice. Given that this is a new area of research associated with logistical, technical and ethical challenges, this multicentre pilot study is essential to establish the feasibility, identify potential challenges and collect pilot data to inform the larger study.

The results from this study will be able to provide direct objective evidence for the timing for cessation of cortical electrical activity (EEG), loss of brainstem auditory pathway transmission to the cortex (ERP), brainstem auditory pathway electrical activity (BAEP/SSEP) and cessation of forward blood flow in the middle cerebral arteries (TCD). The results will not, however, be able to provide definitive data about the presence or absence of consciousness, whole brain function, interneuronal communication and neuronal function at the cellular level or whole brain perfusion. Consciousness, whole brain function, neuronal function at the cellular level and whole brain perfusion would be very challenging to measure non-invasively and in a manner

that respects patient and family privacy at a very difficult time of life. Despite these limitations, this study will provide rich feasibility data in addition to data of interest to neuroscientists, critical care, palliative care and organ donation communities, ethicists, legal scholars, and policy experts. Our pilot multicentre feasibility trial will help inform design and conduct of this larger study, and will provide the first moderately sized prospective multicentre study in humans that will shed light on the neurobiology of the dying process.

FIGURE LEGEND

Figure 1. Timeline outlining study procedures. Abbreviations: BAEP = brainstem auditory evoked potentials; EEG = continuous video-electroencephalography; EP = event-related potentials; SSEP = somatosensory evoked potential; TCD = transcranial doppler; WLSM = withdrawal of life sustaining measures

CONTRIBUTORS

TEG, MS, MM, SD, LN and DD contributed to the conception of the work within this manuscript, development of the final protocol, drafting and revising of the manuscript and final approval of the version to be submitted. GB, EC, JC, MC, NBS, YHC, FDA, SWE, TAF, AK, JK, NBM, JMS, MJS, CW, SS, TB and EC all contributed to revising the manuscript and final approval of the version to be submitted.

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COMPETING INTERESTS

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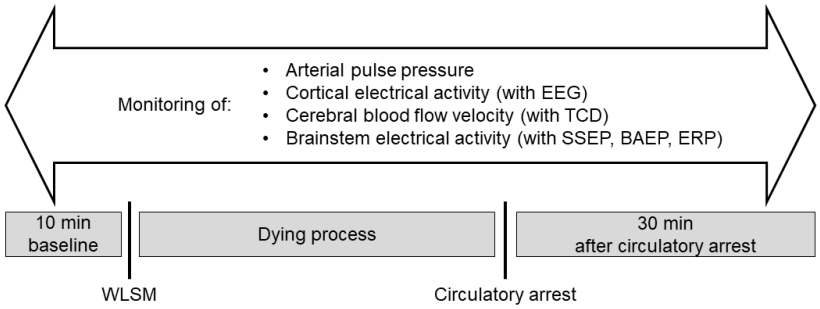

Figure 1. Timeline outlining study procedures. Abbreviations: BAEP = brainstem auditory evoked potentials; EEG = continuous video-electroencephalography; EP = event-related potentials; SSEP = somatosensory evoked potential; TCD = transcranial doppler; WLSM = withdrawal of life sustaining measures

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1, 4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7-8
Objectives	3	State specific objectives, including any prespecified hypotheses	8, 9
Methods			
Study design	4	Present key elements of study design early in the paper	9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	10-11
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	15, 17, 18
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	19
Bias	9	Describe any efforts to address potential sources of bias	Multi-centre
Study size	10	Explain how the study size was arrived at	16
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	15
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	17-21
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	Report numbers of outcome events or summary measures over time	N/A

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	N/A
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	22
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	N/A
Generalisability	21	Discuss the generalisability (external validity) of the study results	6
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.