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


ABSTRACT

Introduction In donation after circulatory determination of death, death is declared 5 min after circulatory arrest. This practice assumes, but does not explicitly confirm, permanent loss of brain activity. While this assumption is rooted a strong physiological 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 haemodynamic monitors in adult patients undergoing planned withdrawal of life sustaining measures in the intensive care units at five hospital sites for 18 months. We will use MATLAB to synchronise 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 (a) proportion of patients with complete waveform recordings and data transfer to coordinating site and (b) time difference between cessation of neurophysiological signals and circulatory arrest. We expect 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, version 1.0, date 19 January 2022.) 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.

Trial registration number NCT05306327.

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 multicentred prospective study design will provide generalisable 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 min after circulatory arrest. While this assumption is rooted in a strong physiological rationale, a lack of neurophysiological evidence regarding cessation of brain activity in humans contributes to ethical concerns and ongoing mistrust of the DCDD process among healthcare and public stakeholders. Healthcare providers may have uncertainty that waiting 5 min after circulatory arrest is sufficient to declare death in DCDD and ensure a permanent cessation of all brain activity prior to organ retrieval.
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-centre study confirmed that waiting 5 min 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-level 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 aetiology of critical illness among different intensive care units (eg, neurological 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 neurophysiological 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 multicentre 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 multi-centred 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: (a) proportion of patients with complete EEG, TCD and arterial pulse pressure waveform; (b) proportion of patients with complete transfer of waveform data to the London Health Sciences Centre (LHSC) site, and challenges to transferring complete waveform data; (c) time difference between circulatory arrest and cessation of EEG and TCD signals; (d) estimate of arterial pulse pressure and blood oxygenation at the time of cessation of EEG and TCD signals; (e) accrual of patients who complete evoked potentials and event-related potentials (ERP) at LHSC site; (f) 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 authorised 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 organisation, 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 (eg, 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 enrol patients from the intensive care units at five participating academic centres (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 >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 neurological criteria or with injuries that anatomically preclude neuromonitoring will be excluded.

**STUDY INTERVENTIONS**

**Continuous video-EEG**

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. Electrode impedances will be maintained within 100–10 000 ohms. Inter-electrode 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. To mitigate artefacts, we will use a non-cephalic channel and standard video monitoring to exclude sources of artefact 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.

**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. 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.

**Haemodynamic monitoring**

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

**Event-related, somatosensory and BAEP**

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 or short-latency SSEP. 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 μs) 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 10 ms from source generators in the brainstem and as late as 300 ms 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 20–35 ms 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 min. For any given patient we will not use more than two neuromonitors (eg, 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 enrolment.

Once neuromonitors are applied, technicians will exit the room and the research team will initiate recordings and collect at least 10 min 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 healthcare 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 guidelines15 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 min 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 min after circulatory arrest to enable procedures for organ retrieval surgery. If any monitoring equipment (ie, 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 synchronisation of neurological and haemodynamic data during data analysis, the clocks on neurological monitors will be synchronised with the haemodynamic 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 II score, Glasgow Coma Scale, organ donation assessment by local organ donation organisation, 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 24 hours prior to WLSM. We will also record sedation score in the 12-hour period prior to WLSM (eg, 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 haemodynamic and neurological waveform data, we will record the following clinical variables during WLSM and for 30 min 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 min following determination of death (5 min in DCDD) and ECG 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 five sites. We expect to enrol 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 enrol <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 enrol 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 analyse 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 summarise the feasibility outcomes. For categorical variables, frequencies and percentages will be tabulated. For continuous variables, means, medians, SD, IQRs, maximum and minimum will be tabulated. We will use MATLAB to synchronise and
process waveform data, and SPSS to compute summary statistics. We will analyse each outcome as follows.

**Patient accrual**

We will compute the proportion of patients who were eligible for enrolment, 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 summarise the reasons for all missing or incomplete EEG/TCD/ERP/SSEP/BAEP and arterial pulse pressure data (eg, 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 synchronised 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. We will pool data across patients to calculate the mean and SD for the sample across patients. Given the difference in patient mix and approaches to WLSM between sites, we will stratify our analysis by site.

The 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. The exact time of electrocerebral inactivity will begin at the onset of <2 μV for at least 60 s 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. The exact time of cessation of cerebral blood flow will begin at the onset of when these criteria are met for at least 60 s and will be determined by two adjudicators qualified in ultrasonography.

3. **Arterial pulse pressure** (ie, circulatory arrest): Defined as a pulse pressure of ≤5 mm Hg that persists for at least 60 s. The exact timing of cessation of arterial pulse pressure will be determined by two blindered adjudicators. Discrepancies will be resolved by consensus by a panel of experts in neurocritical care.

4. **Evoked potentials and ERPs**: 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 40 Hz auditory steady state response which is a type of ERP 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 s and will be determined by two adjudicators.

**Data analysis plan**

For categorical variables, frequencies and percentages will be tabulated. For continuous variables, means, medians, SD, IQRs, maximum and minimum will be tabulated. We will use MATLAB to synchronise and process waveform data, and SPSS 25 to compute summary statistics. We will analyse each outcome as follows:

1. **Patient accrual**: We will compute proportion of patients who were (a) eligible for enrolment, (b) were enrolled, (c) complete full study protocol, (d) 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 (a) spans circulatory arrest, (b) includes data for at least 80% of the planned observation period and (c) 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 synchronised 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 SD/IQR/CI 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 synthesise 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 (TG) 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 enrolment or from the legally authorised substitute decision maker for patients lacking capacity. Elsewhere we have published a detailed ethical analysis of this study’s protocol.

Review of ongoing study activities will occur every 3 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 Programme. 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 organisations, local hospital staff and relevant patient advocacy organisations 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 min 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.

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