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Assessing the relationship between near-infrared spectroscopy derived regional cerebral oxygenation and neurological dysfunction in critically ill adults: a prospective multi-centre protocol, on behalf of the Canadian Critical Care Trials Group

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Supplemental Figure 1.gif	

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5 Title: Assessing the relationship between near-infrared spectroscopy derived
6 regional cerebral oxygenation and neurological dysfunction in critically ill
7 adults: a prospective multi-centre protocol, on behalf of the Canadian
8 Critical Care Trials Group
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For peer review only

Abstract:

Introduction: Survivors of critical illness frequently exhibit acute and chronic neurological complications. The underlying etiology of this dysfunction remains unknown but may be associated with cerebral ischemia. This study will use near-infrared spectroscopy (NIRS) to non-invasively quantify regional cerebral oxygenation (rSO₂) to assess the association between poor rSO₂ during the first 72 hours of critical illness with the development of delirium, as well as long-term sensorimotor and cognitive impairment among intensive care unit (ICU) survivors.

Methods and analysis: This multi-centre prospective observational study will consider adult patients (≥ 18 years old) eligible for enrolment if within 24 hours of ICU admission, they require mechanical ventilation, and/or vasopressor support. For 72 hours, rSO₂ will be continuously recorded, while vital signs (e.g., heart rate) and peripheral oxygenation saturation will be concurrently captured with data monitoring software. Arterial and central venous gases will be sampled every 12 hours for the 72h recording period and will include: pH, partial pressure of oxygen, partial pressure of carbon dioxide, and hemoglobin concentration. Participants will be screened daily for delirium with the confusion assessment method (CAM)-ICU, whereas the brief-CAM will be used on the ward. At 3- and 12-months post-ICU discharge, neurological function will be assessed with the Repeatable Battery for the Assessment of Neuropsychological Status and KINARM robot-based behavioral tasks.

Ethics and Dissemination: The study protocol has been approved in Ontario by a central research ethics board (Clinical Trials Ontario); non-Ontario sites will obtain local ethics approval. The study will be conducted under the guidance of the Canadian Critical Care Trials Group (CCCTG) and the results of this study will be presented at national meetings of the CCCTG for internal

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2
3 peer review. Results will also be presented at national/international scientific conferences. Upon
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5 completion, the study findings will be submitted for publication in peer-reviewed journals.
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8 *Trial Registration:* This trial is registered on clinicaltrials.gov (Identifier: [NCT03141619](https://clinicaltrials.gov/ct2/show/study/NCT03141619)),
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10 registered May 5, 2017.
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13 *Key Words:* Near-infrared spectroscopy; Cerebral oximetry; Cerebral autoregulation; KINARM,
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15 Delirium; CAM-ICU; Post-intensive care syndrome; RBANS
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Strengths and Limitations of this study:

- Potential to replicate our previous finding that poor regional cerebral oxygenation (rSO₂) is an independent risk factor for the development of delirium in a representative cohort of critically ill patients and provide evidence for the utility of rSO₂ monitoring.
- Further assessment of dysfunctional cerebral autoregulation as a potential underlying mechanism associated with poor rSO₂ and the subsequent development of delirium and post-intensive care unit (ICU) neurological impairment.
- Regression analysis will include multiple clinically relevant covariates (e.g., sedative and analgesic medications) to further characterize the hemodynamic and physiological determinants of the near-infrared spectroscopy (NIRS) derived signal as preliminary steps to developing a rSO₂ resuscitation target during critical care.
- Correlating neurophysiological and cognitive performance metrics will further characterize post-ICU outcomes and identify modifiable risk factors (e.g., time spent < optimal mean arterial pressure, disturbed autoregulation duration); however, this study is observational and correlational in nature and will therefore limit causal inferences.
- Further investigation of the determinants of the NIRS signal has the potential to revolutionize critical care by providing clinicians with the ability to determine and maintain individualized blood pressure thresholds to respond to pathological alterations, implement precision-based medicine at bedside, and ensure adequate cerebral oxygenation to preserve neurological function among survivors of critical illness.

Introduction:

Medical advancements in the intensive care unit (ICU) has led to a substantial reduction in mortality rates.^{1,2} However, survivors frequently experience post-intensive care syndrome (PICS), which is characterized by cognitive, psychiatric, and physical impairments.³ These complications have profound effects, including long-term cognitive impairments affecting between 25-75% of survivors,³ and an approximately 50% decrease in full-time employment.⁴ Therefore, modern critical care research should improve our understanding of, and the prevention of, long-term impairments in the growing number of ICU survivors.

A recent systematic review identified prolonged delirium as the most consistent and potentially modifiable risk factor for long-term cognitive impairment.⁵ Patients with delirium experience persistent deficits in various domains, including: memory, executive function, verbal fluency, and attention.⁶⁻⁸ Furthermore, robotic technology has indicated that ICU survivors also develop visuospatial and motor deficits.⁹ Importantly, this population experiences chronic cognitive dysfunction similar to patients with moderate traumatic brain injury or mild Alzheimer's disease, with a duration-dependent effect of delirium on impairments in global cognition and executive function.⁶

Delirium is characterized by reduced awareness, emotional disturbances, restlessness, and incoherence with a 60-87% ICU incidence rate.¹⁰ While risk factors associated with delirium include mechanical ventilation, age, and frailty,¹⁰ the underlying etiology of delirium is poorly understood. Cerebral ischemia is thought to play a central role in delirium development; however, understanding this relationship presents several challenges due to the difficulty of continuously measuring cerebral perfusion in the ICU.

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3 This issue has resulted in a limited number of studies investigating the influence of cerebral
4 perfusion on delirium in critically ill patients (Reviewed in¹¹). Near-infrared spectroscopy
5 (NIRS) is a non-invasive technology that measures regional cerebral oxygenation (rSO₂) as a
6 surrogate marker of cerebral perfusion,^{12,13} as rSO₂ values correlate with other markers of
7 cerebral perfusion, including CT perfusion, jugular venous bulb oxygen saturation, and brain
8 tissue oxygen tension.¹²⁻¹⁴ Therefore, NIRS is an ideal candidate for both ICU research and
9 clinical practice.

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12 Feasibility and single-center prospective ICU studies have been performed with NIRS,
13 discovering that low rSO₂ is an independent risk factor for the development of delirium.^{15,16} A
14 nested cohort in this study demonstrated that impaired cerebral auto-regulation (i.e., the ability to
15 maintain stabilized and adequate cerebral perfusion) is also associated with the development and
16 duration of delirium.^{17,18} While these findings were statistically significant, a multi-centre
17 observational study is necessary for external validation and the study of long-term outcomes.

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20 Our overarching hypothesis is that decreased rSO₂ in the early stages of critical illness leads to
21 the development of delirium, as well as long-term cognitive impairment among survivors. The
22 study objectives are to further establish an association between rSO₂ and delirium, and to
23 identify potential risk factors associated with delirium and long-term cognitive deficits. Overall,
24 elucidating the mechanisms of delirium will allow for the development of preventative
25 treatments to improve outcomes among ICU survivors.

Methods and Analysis:

Patient and Public Involvement: At Kingston Health Sciences Centre (KHSC), our staff includes a patient experience advisor who is a critical care nurse that has been previously admitted with respiratory failure and shock. This experience as a front-line health care professional, as well as an ICU patient, will be invaluable to both patient and public involvement. In addition to the scientific community, patients and their families will also be central to the dissemination of our findings. Participants that selected to be informed of the results will be mailed/e-mailed the published findings upon study completion.

Study locations and participants: An overall visual schematic of the study design is shown in Figure 1. This prospective observational study will take place at 7 sites within Canada. KHSC will serve as the coordinating centre, as the ICU has a history of coordinating academic and industry funded studies and the staff are familiar with the CONFOCAL protocol, as the pilot study¹⁶ was conducted at this site. Patients are considered eligible if they are ≥ 18 years old, have been admitted to the ICU > 24 hours and have respiratory failure requiring invasive mechanical ventilation with an expected duration > 24 hours, and/or have shock of any etiology. Shock will be defined by the need for one of the following vasopressors/inotropes: Dopamine ≥ 7.5 mcg/kg/min, Dobutamine ≥ 5 mcg/kg/min, Norepinephrine ≥ 5 mcg/min, Phenylephrine ≥ 75 mcg/min, Epinephrine at any dose, Milrinone at any dose (if used in conjunction with another agent), Vasopressin ≥ 0.03 u/min (if used in conjunction with another agent), which is adapted from the BRAIN-ICU inclusion criteria.⁶ The exclusion criteria are admission to the ICU > 24 hours, a life expectancy < 24 hours, a primary central nervous system admitting diagnosis (e.g., traumatic brain injury, stroke, subarachnoid haemorrhage), and/or any reason that the subject may not be able to participate in the follow up assessments (e.g., limb amputation, paresis,

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3 neuromuscular disorders). Post-cardiac arrest patients are also excluded from this study.

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5 Additional study sites will include the following: Toronto Western Hospital (Site PI Dr. Victoria
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7 McCredie), Université de Montreal (Montreal, QC; Site PI Dr. Michael Chasse), Victoria
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9 Hospital (London, ON; Site PI Dr. Ian Ball, with co-PIs Dr. Marat Slesserev and Dr. Niamh
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11 O'Reagan), Ottawa General Hospital (Site PI Dr. Shane English), Ottawa Civic Hospital (Site PI
12
13 Dr. Shane English), and Vancouver General Hospital (Site PI Dr. Donald Griesdale). KHSC is
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15 responsible for developing and maintaining the electronic case report forms (eCRF), data
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17 management, and analysis. Recruitment at KHSC began on January 17, 2018.
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24 *Recruitment and consent:* The Queen's University and Affiliated Hospitals Health Sciences
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26 Research Ethics Board will serve as the board of record for the streamlined research ethics
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28 review system (Clinical Trials Ontario) for which KHSC has gained approval; Non-Ontario sites
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30 will obtain local ethics approval. All patients admitted to the ICU will be screened daily for
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32 eligibility. The participant will be approached by a member of the research staff. If the
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34 participant is unable to provide consent, the research staff will approach the Substitute Decision
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36 Maker (SDM). The research coordinator or trained study staff will obtain informed consent and
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38 documentation of the consent process will be noted in the patient's medical chart. As patients
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40 meeting eligibility criteria are unlikely to be able to give informed consent at the time of
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42 enrolment due to their critical condition, we will employ a deferred consent model when
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44 appropriate (e.g., SDMs are frequently in an emotional state and may not be available to be
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46 contacted), which has already been granted local research ethics board approval. When an SDM
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48 is not available to approach, we will enrol the patient and begin trial procedures until the SDM is
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50 available for a consent encounter, targeted to be within 72 hours of enrolment. However, we will
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3 encourage an *a priori* informed consent whenever possible. The SDM response will be used to
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5 continue all trial procedures or any further data collection. If the patient or substitute decision
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7 maker declines enrolment, then the patient will be excluded, and all data obtained using deferred
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9 consent will be confidentially destroyed. In addition, once the patient has regained capacity
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11 according to the medical team, the patient will be approached to affirm or withdraw consent.
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13 Each site will be provided with patient identification numbers, which will be assigned
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15 sequentially when a patient is enrolled and will be used in all study documentation to ensure
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17 patient confidentiality and anonymity. All eligible patients will be recorded on a screening log,
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19 which will include their study ID, date of consent, or reason the patient could not be enrolled.
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21 The de-identified screening log will be forwarded to the lead project coordinator on a monthly
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23 basis. The individual site research coordinators and investigators will be responsible for ensuring
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25 the ethical conduct of this trial, screening patients, obtaining consent, and training of staff as
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27 needed. The principal investigators and co-investigators will review monthly compliance with
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29 the study protocol and recruitment rates.
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36 *Confidentiality:* To ensure patient confidentiality, identifying information will not be collected
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38 on the Case Report Form. Patients will be identified to the coordinating centre only by their
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40 unique study identification number. The site study coordinator will maintain a participant master
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42 list including the participant name and linked study ID. At the end of the study, this master list
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44 will be destroyed. In accordance with current requirements, we will store the de-identified data
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46 for a minimum of 10 years.
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50 **Data Collection:**

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53 *rSO₂, hemodynamics, medications, and clinical characteristics:* Patients will be enrolled within
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55 the first 24 hours of their ICU admission. Immediately following enrolment, the patient will
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3 undergo rSO₂ monitoring. A sensor will be placed in the centre of the patient's forehead, which
4 is attached to the FORESIGHT ELITE oximeter (CASMED, Caster Medical, Canada). This
5 device will provide continuous quantification of rSO₂, every 2 seconds, for 72 hours. To assess
6 the association between hemodynamics and rSO₂ recordings, we will use a commercially
7 available system (Bedmaster, Excel Medical Electronics, FL, USA; or site equivalent) to capture
8 the following vital signs from enrolled patients: heart rate (HR), systolic blood pressure (SBP),
9 diastolic blood pressure (DBP), mean arterial pressure (MAP), and peripheral oxygen saturation
10 (SpO₂). These data are captured locally and uploaded to the eCRF (REDCap). Throughout this
11 72-hour period of recording, we will document administered continuous infusion and intermittent
12 bolus doses of vasoactive and sedative/analgesic medications, which will be converted to either
13 "fentanyl equivalents" for narcotics, or "midazolam equivalents" for benzodiazepine
14 medications. These conversion formulas have been previously described.¹⁹ Severity of illness
15 will be measured during the first 24 hours of ICU admission using the Acute Physiology and
16 Chronic Health Evaluation II score (APACHE II). Pre-existing frailty will be assessed upon
17 enrolment using the clinical frailty scale,²⁰ which is 9-point scale (e.g., 1 = very fit to 9 =
18 terminally ill). All clinical data will be captured on the eCRF.

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41 *Central venous and arterial blood collection:* Both arterial and central venous gases will be
42 sampled every 12 hours during the 72h period of rSO₂ recording and will include: pH, partial
43 pressure of oxygen (pO₂), partial pressure of carbon dioxide (pCO₂), and hemoglobin
44 concentration (Hb). These blood samples will be collected only if a central line (PICC, internal
45 jugular, subclavian) and arterial line are *already* in place.

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53 *Delirium screening:* Patients will be assessed daily for delirium throughout their entire hospital
54 stay (ICU and ward; up to day 30) using validated screening tools; the Confusion Assessment
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3 Method (CAM)-ICU²¹, as well as the brief Confusion Assessment Method (bCAM)²² which will
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5 be administered on the ward. From the CAM-ICU, the CAM-ICU 7 (i.e., 7-point delirium
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7 severity scale) will also be documented (i.e., 0-2: no delirium, 3-5: mild to moderate delirium,
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9 and 6-7: severe delirium).²³ The ICU discharge day will be considered to be the day that the
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11 attending writes orders to discharge, in order to avoid the influence of delayed discharge.
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15 *Determination of pre-existing cognitive impairment:* Our pilot study¹⁶ excluded 10% of patients
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17 with a documented history of cognitive impairment in their medical chart, which may limit
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19 external validity. Importantly, individuals may have substantial cognitive impairment prior to
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21 enrolment but did not receive any formal diagnosis. To address this potential confound, all
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23 patients will be assessed, upon enrolment, using the clinical dementia rating (CDR) scale.²⁴ The
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25 CDR is a scale from 0 (Normal) to 3 (severe dementia) that is calculated from a standardized
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27 scoring sheet completed by interviewing a patient or their caregiver. All staff completing the
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29 interview and scoring sheet will undergo rigorous online training and pass a certification exam.
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31 A diagnosis of pre-existing cognitive impairment will be defined as a CDR >1.
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40 **3- and 12-Month Follow Up:**

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42 *Neuropsychological assessment: Repeatable Battery for the Assessment of Neuropsychological*
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44 *Status (RBANS):* Participants will complete a 3- and 12-month follow up assessment in which
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46 the RBANS will be administered by a trained researcher. The RBANS assesses global cognition,
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48 as well as several subdomains (i.e., immediate and delayed memory, visuospatial/constructional,
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50 language, and attention). These indices have been described previously,²⁵ and survivors will be
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52 compared to age-matched controls. To improve follow up rates, in home/hospital testing will be
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3 performed for individuals not able to return for laboratory assessment. Participant scores are
4 converted to standardized values in which the normative range will be considered a mean of
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6 100 \pm 24.75 (1.65 SD). Participants that score >75 will not be considered impaired, as these
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8 subjects are performing within or above the normative range. The RBANS assessment requires
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10 ~20-30 minutes to complete.
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15 *KINARM Assessment:* Participants (from the Kingston region only) will complete a 3- and 12-
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17 month follow up assessment using the End-Point bimanual KINARM robot (BKIN
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19 Technologies, Kingston). With each hand, the seated subject grasps a handle attached to a planar
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21 robotic device that permits movements in the horizontal plane with an integrated virtual reality
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23 system that presents objects in the horizontal plane (Figure 2). Subjects will perform a
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25 behavioural battery to quantify a broad range of sensorimotor, and cognitive function using their
26
27 upper limbs. A trained operator selects a task from the software menu, reads the standardized
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29 instructions, and then monitors performance in real-time. We will administer 7 tasks from the
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31 KINARM Standard Tests™ including: Spatial Span (SS, Figure 3A), Visually Guided Reaching
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33 (VGR, Figure 3B), Reverse Visually Guided Reaching (RVGR, Figure 3B), Ball on Bar (BonB,
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35 Figure 3C), Arm Position Matching (APM, Figure 3D), Object Hit (OH, see Figure 3E), Object
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37 Hit and Avoid (OHA, see Figure 3F). Each task has been previously described,²⁶ and quantifies
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39 subject performance using approximately 6 to 12 metrics per task. Each metric is converted into
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41 normalized units based on healthy subject performance, considering the influence of sex, age,
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43 and handedness (0 is mean performance and ± 1 is a standard deviation from the mean). For each
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45 task, a task score will also be generated to provide a global performance measure with values
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47 that are equivalent to standard deviation units with zero specifying best possible performance,
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49 and higher values indicating worse performance. Therefore, performance will be considered
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3 abnormal if the task score is outside the +1.96 range (i.e., 5th percentile). The task score has been
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5 previously described.²⁷ The KINARM assessment takes ~45 minutes to complete.
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8 **Sample Size Calculation:**

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11 *Primary Outcome:* Our overall hypothesis is that poor cerebral perfusion contributes to delirium
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13 and long-term cognitive impairment. For study purposes, we define poor cerebral perfusion as
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15 the composite of 1) low mean rSO₂, 2) duration of impaired cerebral autoregulation, and 3) time
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17 outside individualized optimal MAP (MAP_{OPT}), which will be discussed in more detail in the
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19 statistical plan section. We acknowledge that this is an imperfect measure of cerebral perfusion.
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21 However, this is a comprehensive, continuous, and non-invasive assessment of cerebral
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23 perfusion. For our primary outcome (CAM-7 delirium severity score), we plan to assess
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25 approximately 400 patients, to allow 10 degrees of freedom for our 3 measures of perfusion (i.e.,
26
27 mean rSO₂, duration of disturbed cerebral autoregulation, duration outside MAP_{OPT}) and
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29 controlling for the 9 covariates (see below). The 10 degrees of freedom will allow us to model
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31 non-linear relationships between the 3 measures of cerebral perfusion and delirium severity. This
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33 sample size achieves 90% power to detect an R² of 0.050 collectively among these measures of
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35 cerebral perfusion and using an F-test with a significance level (alpha) of 0.050 (see Figure 4). In
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37 order to have ≥400 patients to assess, we will enrol 500 patients, as our prior work has
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39 demonstrated that ~20% of patients remain comatose (RASS = -4 or -5) during their entire ICU
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41 stay¹⁶, and cannot be assessed for delirium.
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49 *Secondary Outcomes-Physiological determinants of rSO₂ and neurological outcomes*

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52 For evaluating the determinants of the rSO₂ signal, we will assess the association between each
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54 of the 9 pre-specified candidate predictors of rSO₂ after controlling for the 4 co-variates (see
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below for co-variables). We will use a Bonferroni correction ($0.05/9=0.0056$) to control for multiple testing. With the 500 patients recruited, and a multivariate regression model that includes 13 independent variables, this testing strategy will provide 90% power to identify any predictor that explains an additional 3.2% of the variance of rSO_2 after controlling for the other variables in the model. This sample size is sufficient to identify independent significant predictors that account for a small-moderate degree of variance in the overall rSO_2 signal. Given our overall sample size of 500 patients recruited, we are anticipating 350 survivors, assuming a 30% mortality rate observed in our prior study, which will provide sufficient power to detect important predictors of long-term neurological outcomes. These have been intentionally not specified *a priori*, as this will depend on our findings related to cerebral perfusion and delirium.

All sample size calculations were conducted using Power Analysis and Sample Size Software (Version 15).²⁸

Statistical Plan:

Quantification of disturbed cerebral autoregulation: Cerebral autoregulation will be evaluated by computing customized algorithms (MATLAB, MathWorks, MA, USA) of the time-varying Spearman correlation coefficients between rSO_2 and MAP (i.e., cerebral autoregulation index, COx) with a moving time window advanced in 1 min steps over the 72-hour period of recording. This cerebral autoregulation assessment has been previously described¹⁸ and a visual representation can be observed in Figure 5. In addition, we will perform the COx across varying window lengths to further assess the optimal window length of recording (e.g., 5, 10, 30, 60, 120, 240, 300-minute windows). Positive COx values (i.e., MAP and rSO_2 move in the same direction) reflect dysfunctional cerebral autoregulation, whereas negative (i.e., MAP and rSO_2 move in the opposite direction) and near zero (< 0.3) indicate intact cerebral autoregulation.

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3 However, we will define cerebral autoregulation dysfunction by using a statistical significance
4 threshold for positive COx correlation values ($p < 0.0001$). Cumulative duration of disturbed
5 autoregulation will be given by the duration of time spent with a significant positive correlation
6 throughout the period of neuromonitoring. Computer algorithms for COx will be developed and
7 implemented blind to the neurological status of enrolled patients.
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15 *Estimating optimal MAP:* To calculate the individualized optimal MAP (MAP_{OPT}), the computed
16 COx values will be binned by the average MAP value in their respective moving windows in 5
17 mmHg bins.²⁹ An alternative strategy will also be implemented. We will invert the MAP_{OPT}
18 binning procedure by binning MAP values by their corresponding COx values in sequential 0.05
19 bins of Spearman correlation coefficients ranging from -1 to +1. This procedure has been
20 previously described.¹⁸
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30 *Assessment of primary outcome:* Multivariate linear regression will be used to characterize the
31 association between adequate cerebral perfusion (as measured using duration of time (minutes)
32 outside of MAP_{OPT} , mean rSO_2 , and duration of disturbed cerebral autoregulation) and delirium
33 severity throughout a patient's ICU stay to determine if poor cerebral oxygenation is an
34 independent predictor of delirium. We will estimate the unadjusted effect of each individual
35 predictor on delirium severity (i.e., cumulative CAM-7 scores per patient). The simultaneous
36 multivariate regression model will adjust for the following covariates due to their potential
37 associations with delirium: a history of hypertension, a history of alcohol abuse, total sedative
38 dose (in midazolam equivalents), total narcotic dose (in fentanyl equivalents), severity of illness
39 (APACHE II scores), pre-existing cognitive impairment (CDR score), length of ICU stay, frailty,
40 (clinical frailty scale) and blood urea nitrogen. The multivariable model will provide the adjusted
41 regression coefficients after controlling for all predictors included in the model. All covariates
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3 included in regression modeling have been chosen *a priori* based on clinical judgment and
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5 previous research.^{16,30} Model diagnostics will be conducted to assess the underlying assumptions
6
7 of linear regression (i.e., linearity, normally distributed residuals, equal variances, and lack of
8
9 multicollinearity) for all models. Multiple imputation strategies will be applied at the time of the
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11 regression modeling to account for any missing data and reduce bias associated with excluding
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13 patients due to partially collected data.
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18 *Secondary outcomes:*
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21 *Determinants of rSO₂:* To assess the hemodynamic and physiological determinants of rSO₂ at the
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23 patient level, multiple linear regression will be performed using the patient average of each
24
25 variable over the 72-hour data collection period. The following predictors will be included in the
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27 regression model: HR, SpO₂, MAP, arterial, and venous blood gas data (i.e., pH, pO₂, and
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29 pCO₂), central venous oxygen saturation, and Hb concentration. In addition, the multivariate
30
31 model will control for the following covariates associated with cerebral perfusion: age,³¹ as well
32
33 as total sedative, narcotic, and vasopressor dosing. Simultaneous multiple linear regression with
34
35 adjustment for all aforementioned covariates will be implemented. As stated for the primary
36
37 outcome regression analysis, model diagnostics will be performed. Furthermore, the relationship
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39 between the determinants of the NIRS-derived rSO₂ signal may vary over time (see Figure 6 and
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41 Supplemental Movie 1). Therefore, a repeated measures analysis will also be performed by using
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43 multilevel modeling with 6 observations reflecting each 12-hour period during the 72-hour data
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45 collection period (with time coded as 0 – 5, so the intercept equals baseline/time of enrolment)
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47 nested within each subject. The predictors will be the same as the regression model but allowed
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49 to be time varying across the 6 observation points. This analysis will assess if within patient
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3 changes in the predictors correlate with changes in rSO₂, and if these associations are modified
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5 by fixed patient characteristics, such as age.
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8 *Assessing if poor cerebral perfusion during critical illness is a significant predictor of long-term*
9 *neurological dysfunction among ICU survivors:* Multiple linear regression analysis will be used
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11 to assess if impaired cerebral perfusion (i.e., time below MAP_{OPT}, mean rSO₂, and duration of
12
13 disturbed cerebral autoregulation) is associated with RBANS global cognition scores at 3- and
14
15 12-months post-ICU discharge. We will use the following clinical covariates collected on
16
17 admission (i.e., pre-existing cognitive impairment, age, severity of illness, frailty) and data
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19 collected within the first 72 hours of the patients' ICU stay (i.e., narcotic dosing and
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21 benzodiazepine dosing). All covariates will be adjusted for in separate regression models for the
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23 cognitive outcomes at 3- and 12-months post-ICU discharge. If global cognition is significantly
24
25 predicted by the time below MAP_{OPT}, we will conduct an exploratory analysis of the RBANS
26
27 subdomains of cognition (i.e., delay and immediate memory, language, attention,
28
29 visuospatial/constructional) adjusting for the aforementioned covariates to further explore
30
31 specific areas of impairment observed among survivors of critical illness. Only patients assessed
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33 at KHSC will undergo KINARM testing, so this data will be assessed with descriptive statistics
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35 only to avoid any potential bias.
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DISCUSSION

This multicentre observational study will extend our preliminary findings of reduced rSO₂ as an independent risk factor for the development of delirium during critical illness. With the proposed larger sample size, we will not only be able to replicate and validate this completely novel finding, but we will also be able to further characterize the physiological determinants of rSO₂ in a representative cohort. Furthermore, this study will have the potential to identify novel pathophysiological mechanism associated with the development of delirium and long-term neurological dysfunction among ICU survivors. These findings will inform the next phase of this research program: a proof-of-principal study, aimed at devising strategies to optimize rSO₂. It will lay the foundation for a larger interventional study designed to assess whether optimization of rSO₂ can reduce delirium and improve long-term neurological outcomes for patients.

Ethics and Dissemination:

Risks/Ethical Considerations: Ethics approval will be obtained prior to the commencement of screening and enrolment at each site. There are no assumed risks associated with the proposed assessment procedures, as this study only involves a small amount of bloodwork, which will only be collected if a central line and arterial line are *already* in place. Furthermore, results from our pilot study demonstrated that non-invasive monitoring of cerebral oxygenation, while using a deferred consent model, does not interfere with patient care or management.¹⁵ Research participants and their SDMs will be informed that enrolment in this study will not affect their care in any way, and that they have the right to refuse participation or withdraw at any time.

Dissemination of results: The results of this study will be presented at national meetings of the Canadian Critical Care Trials Group. Prior to submitting any manuscript for publication, it will undergo rigorous internal peer review by this group of critical care experts. Our study group has a long track record of presenting our data at national and international critical care conferences. We anticipate the preliminary results of this research program will also be presented at these conferences (e.g., American Delirium Society). The final study results will be submitted for publication to high impact journals.

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List of Abbreviations

APM: Arm Position Matching

BonB: Ball on Bar

bCAM: Brief Confusion Assessment Method

CDR: Clinical Dementia Rating Scale

COx: Cerebral Oximetry Index

Hb: Hemoglobin Concentration

HR: Heart Rate

KHSC: Kingston Health Sciences Centre

KINARM: Kinesiological Instrument for Normal and Altered Reaching Movement

ICU: Intensive Care Unit

MAP: Mean Arterial Pressure

MAP_{OPT}: Optimal Mean Arterial Pressure

NIRS: Near-infrared Spectroscopy

OH: Object Hit

OHA: Object Hit and Avoid

pCO₂: Arterial Partial Pressure of Carbon Dioxide

PICS: Post-intensive Care Syndrome

pO₂: Arterial Partial Pressure of Oxygen

RASS: Richmond Agitation and Sedation Scale

RBANS: Repeatable Battery for the Assessment of Neuropsychological Status

rSO₂: Regional Cerebral Oxygenation

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3 RVGR: Reverse Visually Guided Reaching
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5 SpO₂: Peripheral Oxygen Saturation
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7 SS: Spatial Span
8

9 SDM: Substitute Decision Maker
10

11 VGR: Visually Guided Reaching
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14
15 **Authors' contributions:**

16 MDW participated in study design, statistical planning, and drafting of the manuscript.

17 JK participated in study design and drafting of the manuscript.
18

19 KL participated in study design and drafting of the manuscript.
20

21 DM participated in study design and drafting of the manuscript.
22

23 JM participated in study design and drafting of the manuscript.
24

25 MH participated in study design and drafting of the manuscript.
26

27 SHS participated in study design and drafting of the manuscript.
28

29 AD participated in sample size calculations and finalizing of the statistical plan.
30

31 JAJ participated in statistical planning and drafting of the manuscript.
32

33 IB participated in study design and drafting of the manuscript.
34

35 MS participated in study design and drafting of the manuscript.
36

37 NO participated in study design and drafting of the manuscript.
38

39 SE participated in study design and drafting of the manuscript.
40

41 VM participated in study design and drafting of the manuscript.
42

43 MC participated in study design and drafting of the manuscript.
44

45 DG participated in study design and drafting of the manuscript.
46

47 JGB is the primary investigator. He participated in study design and drafting of the manuscript.
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49

50
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52
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3 recipient. The funding agencies had no role in the design of this study, data collection, or data
4 analysis.
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8 **Competing interests statement.**
9

10 Mr. Michael D. Wood has nothing to disclose.

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27 Dr. Shane English has nothing to disclose.

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Figure Legends:

Figure 1. A visual representation of the CONFOCAL2 study design from enrolment to 3- and 12-month follow up assessments.

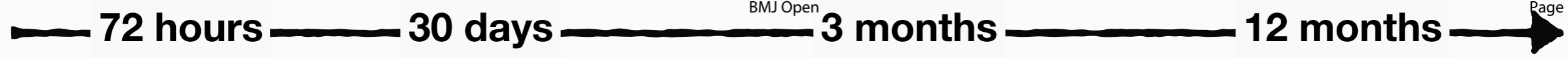
Figure 2. Three-dimensional animated representation of the KINARM End-Point robotic set-up used at 3- and 12-month follow up assessments.

Figure 3. Visual representation of the administered KINARM behavioral battery, where panels A-F represent individual tasks. Dark blue lines represent the bimanual robotic limbs, with connected red circles indicating robotic joints which permit movement of the KINARM. *Note.* While each panel includes a view of the participant's arms, subjects do not see their arms throughout task completion. Instead, they are virtually represented as white circles (A-D) or green paddles (E-F). **A.** Spatial Span (SS). Participants are instructed to memorize a sequence (represented as numbered blue squares) on a 3x4 grid. The task begins with a sequence length of 3 and participants must replicate the sequence using their dominant hand. Sequence length is increased/decreased by 1 unit for every correct/incorrect replication, up to a maximum sequence length of 12, with a total of 17 trials. This task assesses visuospatial working memory. **B.** Visually Guided and Reverse Visually Guided Reaching (VGR and RVGR). Participants are instructed to move the robot to one of four targets, indicated by red circles, and back to the home position (i.e., middle target). In VGR, participant's movement (white arrow) is identical to visual feedback (yellow arrow). In RVGR, virtual feedback is mirrored/inverted (blue arrow) to the actual hand position, requiring participants to initiate corrective movements in the opposite direction. This task assesses visuomotor abilities³² and cognitive override (RVGR).³³ *Note.* Red lines visually represent participant hand paths throughout the entire task. **C.** Ball on Bar (BonB). Participants are instructed to use both hands to balance a virtually represented ball on top of a vertical bar connecting both hands, while sequentially moving to one of four targets (red circles) as quickly and accurately as possible. This task assesses bimanual coordination.³⁴ *Note.* Red lines represent expected hand path of participant. **D.** Arm Position Matching (APM). The KINARM robot moves the participant's dominant hand to one of four targets (blue circles), with the path to these targets represented by blue lines. Participants are instructed to mirror match the movement with their dominant arm, which assess using proprioception.³⁵ *Note.* Red lines represent participant's hand path, and red circles represent the target locations. **E.** Object Hit (OH). Participants hands are visually represented as green paddles and they are instructed to hit targets (i.e., red circles) away from themselves. These targets fall from the top of the screen with greater frequency and speed to increase difficulty over time. White arrows indicate movement of the targets toward the participant. This task assesses rapid decision-making, bimanual sensorimotor abilities, and visuospatial attention.³⁶ **F.** Object Hit and Avoid (OHA). Participants are asked to remember two target shapes and instructed to hit these targets while also avoiding all other objects (i.e., distractors). White arrows indicate movement of the various objects. This task is similar to OH, with additional assessment of higher executive function.³⁷ *Note.* The participant is briefly shown the two targets at the start of the task and they do not appear on screen throughout task duration.

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3 **Figure 4.** A power curve indicating the study sample size, and the respective statistical power, to
4 assess the primary study outcome. *Note.* Red dots represent the sample size needed for a given
5 statistical power. The primary sample size was calculated using the following multivariate
6 regression model parameters: 10 independent variables tested, controlling for 9 additional
7 covariates, power = 0.90, $R^2 = 0.050$, $\alpha = 0.05$, which would require a sample size of 400.
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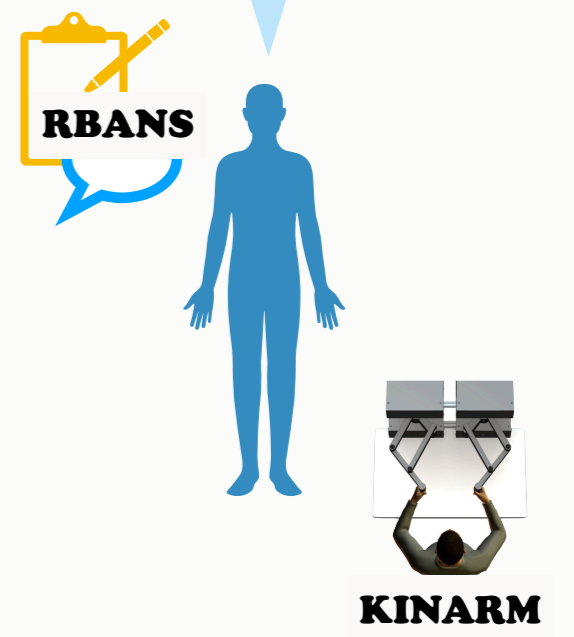
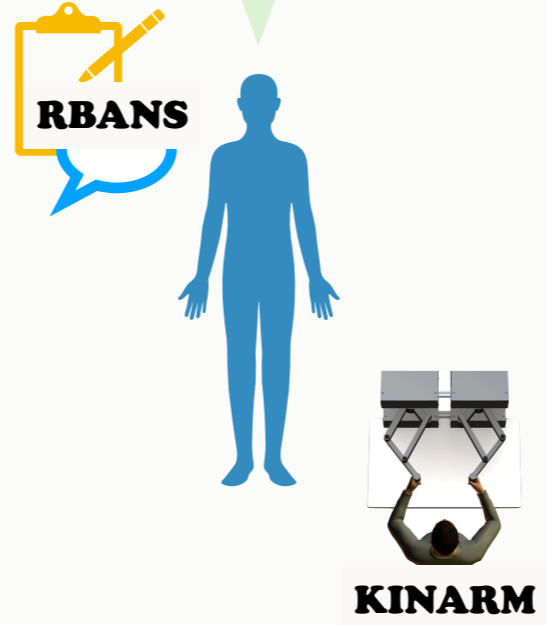
10 **Figure 5A.** Simplified line graph (24 hours instead of the full 72 hour recording period)
11 illustrating the sliding window correlation between mean arterial pressure and regional brain
12 tissue oxygenation for an individual patient over a 24 period of recording. *Note.* The black
13 rectangle represents a 60-minute window that moves forward 1-minute at a time until the
14 recording period is completed. **B.** Scatter plot illustrating a time dependent positive association
15 between mean arterial pressure and regional brain tissue oxygenation. *Note.* Black dots represent
16 data collected for an individual patient over 24 hours, with the blue line representing a linear
17 model fit to the data, and the grey shaded region representing the 95% confidence interval. **C.**
18 Scatter plot indicating the time varying association between mean arterial pressure and regional
19 brain tissue oxygenation represented as the cerebral oximetry index (COx) over an individual
20 patient's 24-hour recording period. *Note.* A positive Cox values (>.3) represents dysfunctional
21 cerebral autoregulation, with negative or near zero values indicating intact cerebral
22 autoregulation.
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27 **Figure 6.** Line graph of the high frequency vital sign recordings indicates the highly variable
28 relationships with regional brain tissue oxygenation over the 72-hour period of recording. *Note.*
29 The figure represents a single patient's ICU recording. rSO_2 = Regional brain tissue oxygenation;
30 HR = Heart rate; SpO_2 = Arterial oxygen saturation; artMAP= Mean arterial pressure from an
31 arterial line.
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NIRS



>18 years old	Neurological/ neurosurgical admitting diagnosis
>24hr mechanical ventilation due to respiratory failure	<24hr life expectancy
Shock	Inability to participate in follow-up

Covariates Collected

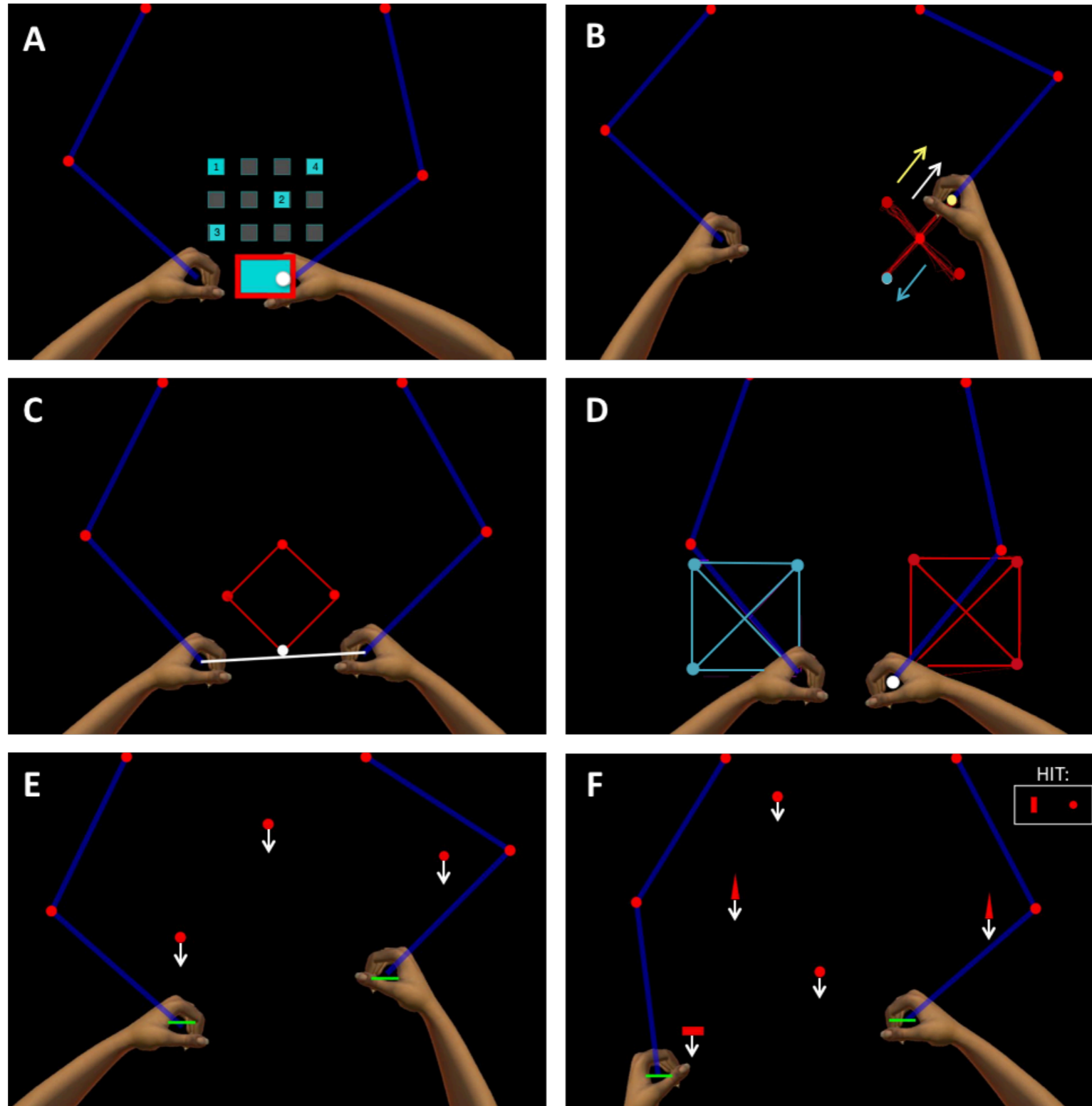


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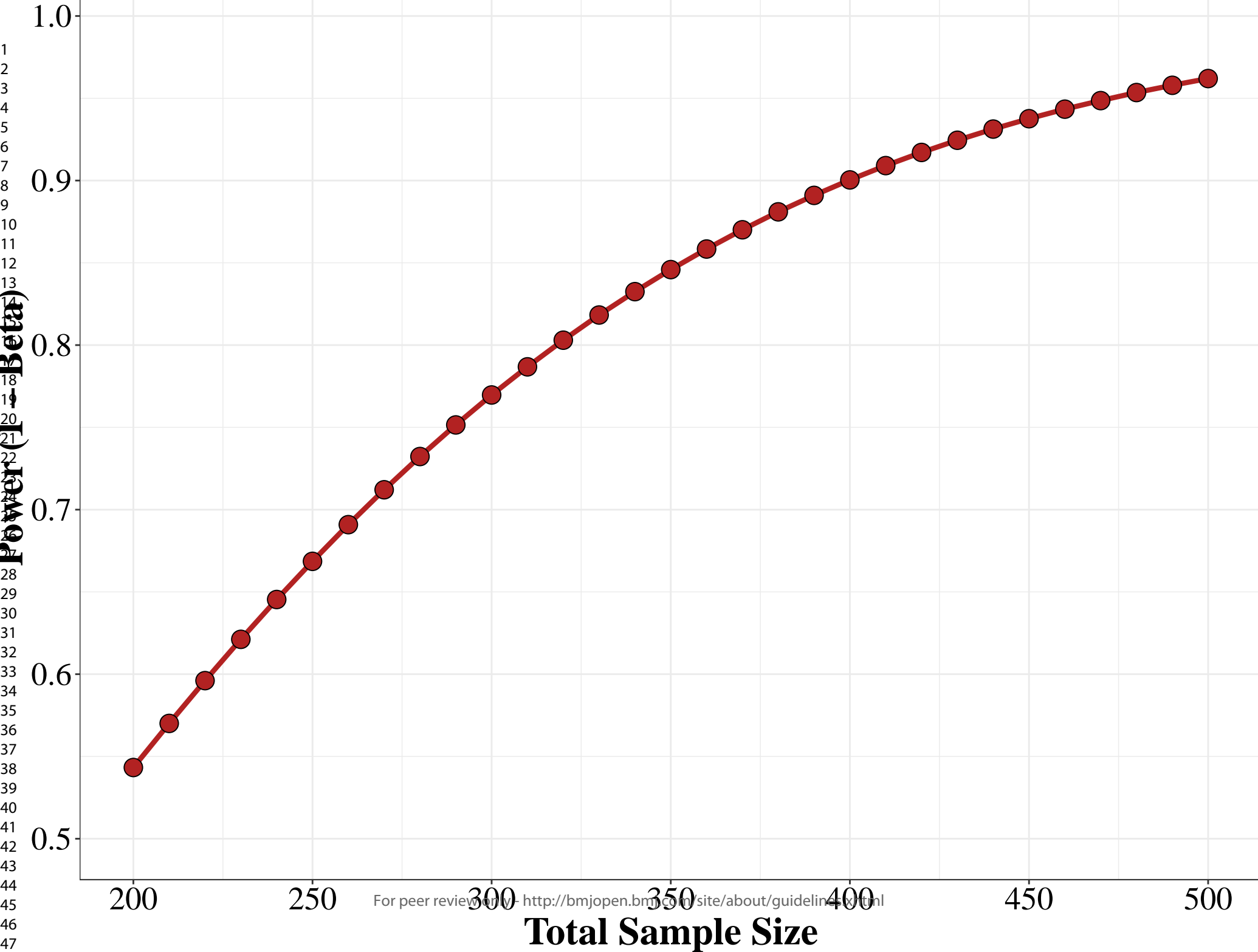


Figure 2. Three-dimensional animated representation of the KINARM End-Point robotic set-up used at 3- and 12-month follow up assessments.

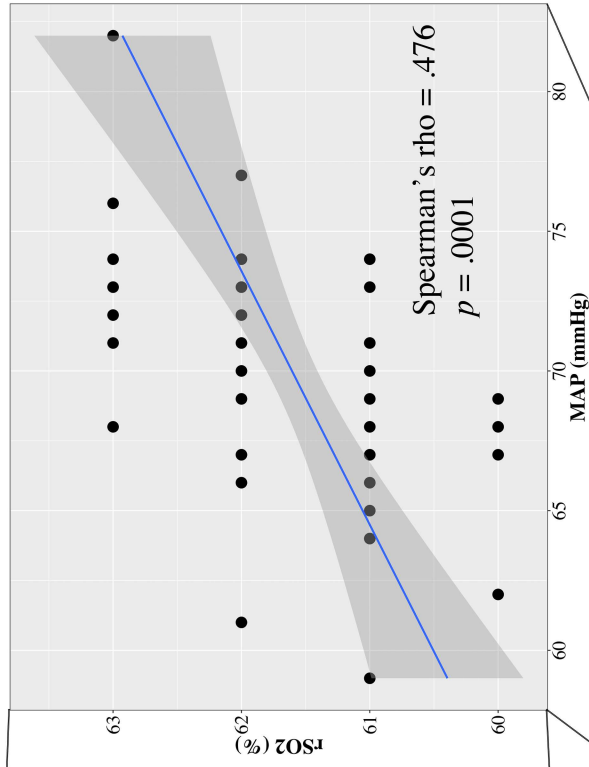
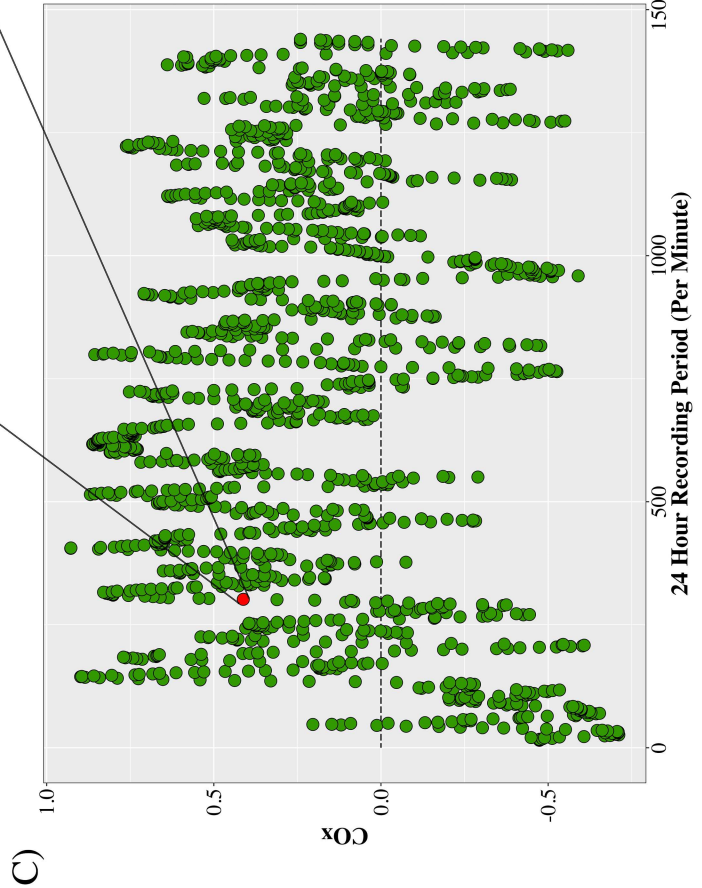
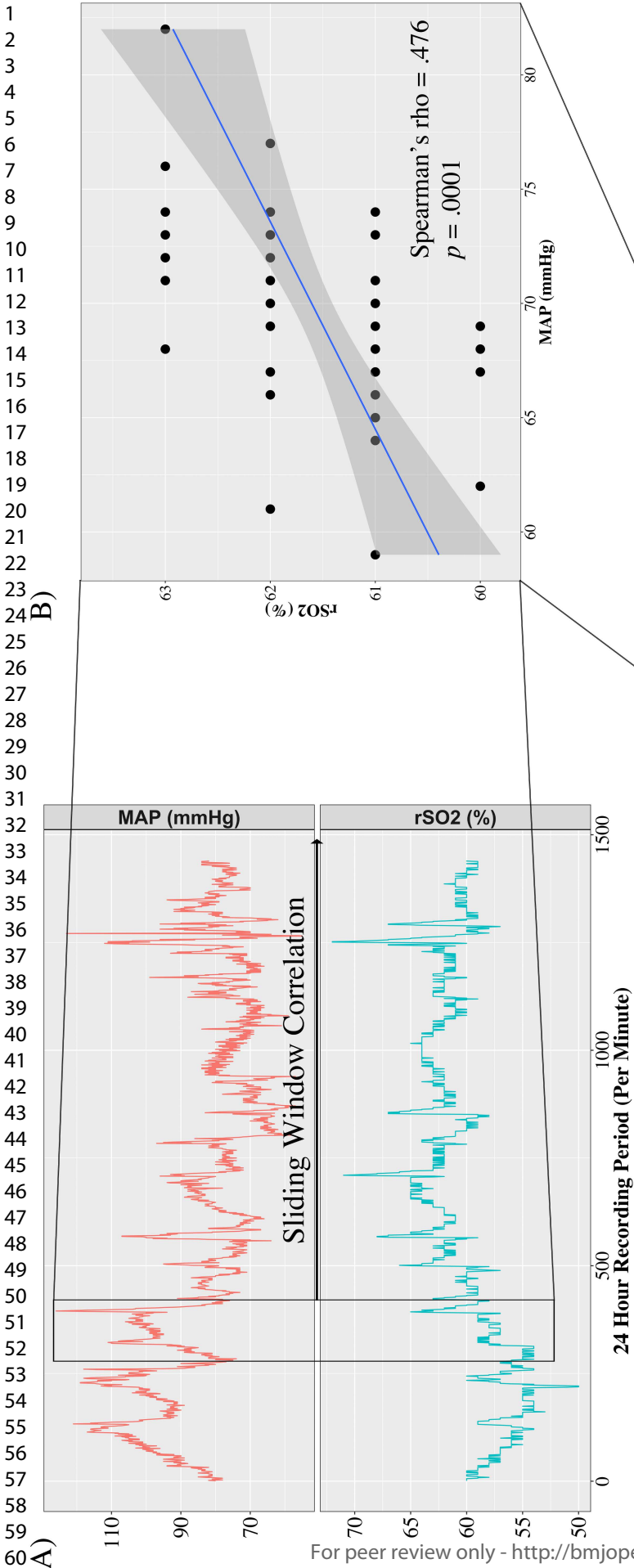
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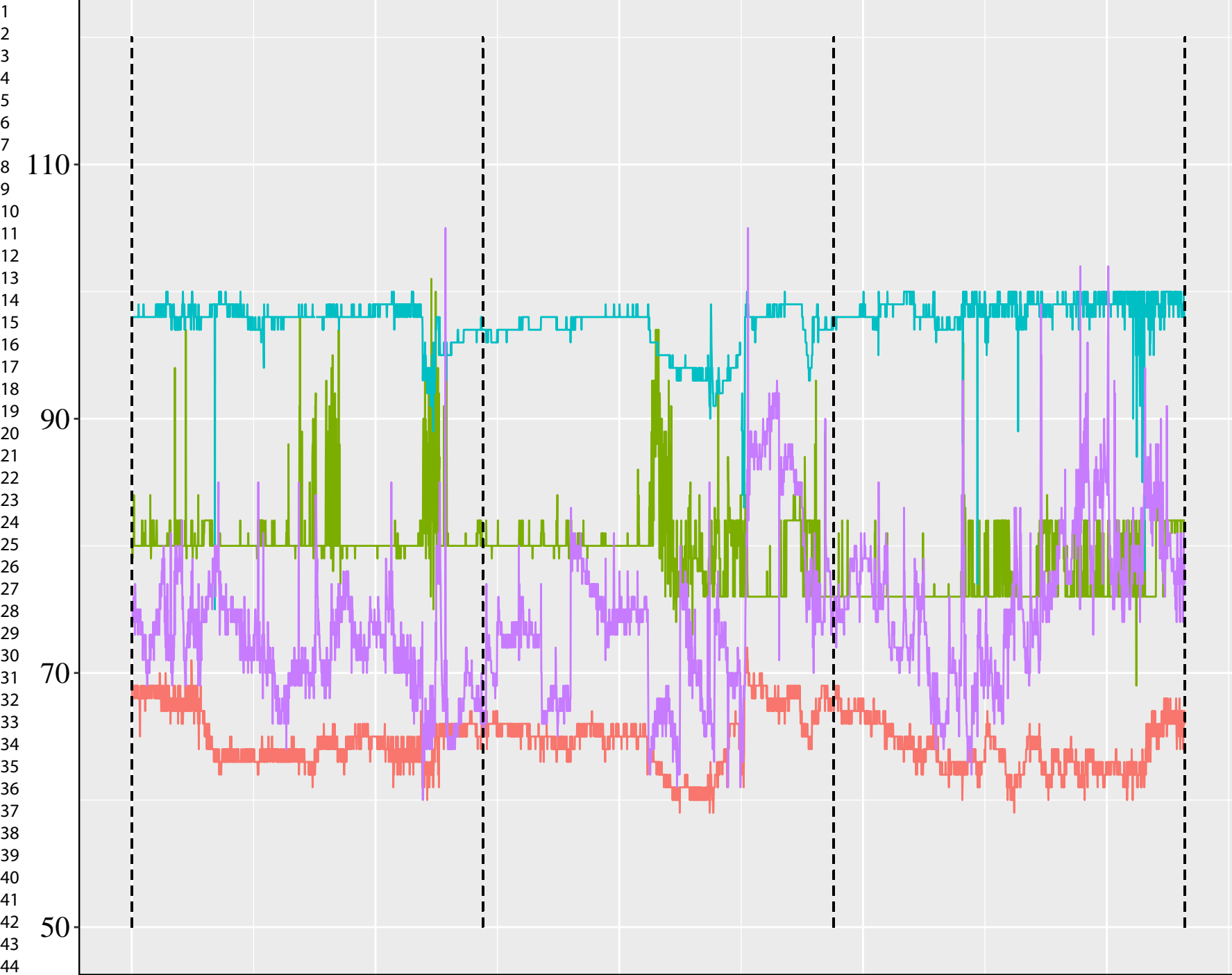
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Enrolment 24 Hours 48 Hours 72 Hours



Variables

- rSO2 (%)
- HR (bpm)
- SpO2 (%)
- artMAP (mmHg)



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page Number on which item is reported
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	25-26
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-2,25
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	25-26
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	9-10
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6-7
	6b	Explanation for choice of comparators	6-7
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	N/A
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	16-18

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10-13
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	14-15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	14-15
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	N/A
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			

1 2 3 4 5 6 7 8 9 10 11	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10-13
12 13 14 15 16 17		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	14-15
18 19 20 21 22 23 24 25	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8-10
26 27 28 29 30 31	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15-18
32 33 34		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15-18
35 36 37 38 39 40		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15-18
41 42	Methods: Monitoring			
43 44 45 46 47 48 49 50 51 52	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
53 54 55 56 57 58 59 60		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	20
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	9,20
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9-10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9-10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	26
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	10
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	20

	31b	Authorship eligibility guidelines and any intended use of professional writers	20
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	20
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

BMJ Open

Assessing the relationship between near-infrared spectroscopy derived regional cerebral oxygenation and neurological dysfunction in critically ill adults: a prospective observational multi-centre protocol, on behalf of the Canadian Critical Care Trials Group

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Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Neurology
Keywords:	Near-infrared spectroscopy, Cerebral autoregulation, KINARM, Delirium, Post-intensive care syndrome, RBANS
Note: The following files were submitted by the author for peer review, but cannot be converted to PDF. You must view these files (e.g. movies) online.	

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Supplemental Figure 1.gif

SCHOLARONE™
Manuscripts

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4 1
5 2 Title: Assessing the relationship between near-infrared spectroscopy derived
6 3 regional cerebral oxygenation and neurological dysfunction in critically ill
7 4 adults: a prospective observational multi-centre protocol, on behalf of the
8 5 Canadian Critical Care Trials Group
9 6
10 7

11 8 Authors: The Cerebral Oxygenation and Neurological Outcomes Following
12 9 Critical Illness (CONFOCAL) Research Group
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14 11

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For peer review only

Abstract:

Introduction: Survivors of critical illness frequently exhibit acute and chronic neurological complications. The underlying etiology of this dysfunction remains unknown but may be associated with cerebral ischemia. This study will use near-infrared spectroscopy (NIRS) to non-invasively quantify regional cerebral oxygenation (rSO₂) to assess the association between poor rSO₂ during the first 72 hours of critical illness with delirium severity, as well as long-term sensorimotor and cognitive impairment among intensive care unit (ICU) survivors. Further, the physiological determinants of rSO₂ will be examined.

Methods and analysis: This multi-centre prospective observational study will consider adult patients (≥ 18 years old) eligible for enrolment if within 24 hours of ICU admission, they require mechanical ventilation, and/or vasopressor support. For 72 hours, rSO₂ will be continuously recorded, while vital signs (e.g., heart rate) and peripheral oxygenation saturation will be concurrently captured with data monitoring software. Arterial and central venous gases will be sampled every 12 hours for the 72h recording period and will include: pH, partial pressure of oxygen, partial pressure of carbon dioxide, and hemoglobin concentration. Participants will be screened daily for delirium with the confusion assessment method (CAM)-ICU, whereas the brief-CAM will be used on the ward. At 3- and 12-months post-ICU discharge, neurological function will be assessed with the Repeatable Battery for the Assessment of Neuropsychological Status and KINARM sensorimotor and cognitive robot-based behavioral tasks.

Ethics and Dissemination: The study protocol has been approved in Ontario by a central research ethics board (Clinical Trials Ontario); non-Ontario sites will obtain local ethics approval. The study will be conducted under the guidance of the Canadian Critical Care Trials Group (CCCTG) and the results of this study will be presented at national meetings of the CCCTG for internal

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3 72 peer review. Results will also be presented at national/international scientific conferences. Upon
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5 73 completion, the study findings will be submitted for publication in peer-reviewed journals.
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8 74 *Trial Registration:* This trial is registered on clinicaltrials.gov (Identifier: [NCT03141619](https://clinicaltrials.gov/ct2/show/study/NCT03141619)),
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10 75 registered May 5, 2017.
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13 76 *Key Words:* Near-infrared spectroscopy; Cerebral oximetry; Cerebral autoregulation; KINARM,
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15 77 Delirium; CAM-ICU; Post-intensive care syndrome; RBANS
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3 81 **Strengths and Limitations of this study:**
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- 6 82 • Potential to replicate our previous work in a representative cohort and further assess the
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8 83 association between poor regional cerebral oxygenation (rSO₂) and ICU associated.
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11 84 • Further assessment of dysfunctional cerebral autoregulation as a potential underlying
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13 85 mechanism associated with the development of delirium and post-intensive care unit
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15 86 (ICU) impairment.
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18 87 • Using multiple regression to further characterize the physiological determinants of the
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20 88 near-infrared spectroscopy (NIRS) derived signal has the potential to lead to the
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22 89 development of a novel resuscitation target during critical care.
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25 90 • Although this study is observational in nature, which limits causal inferences, correlating
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27 91 neurophysiological and cognitive performance metrics may identify modifiable risk
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29 92 factors (e.g., disturbed autoregulation duration) during critical care.
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32 93 • Understanding the determinants of the NIRS signal may revolutionize critical care by
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34 94 providing clinicians with the ability to implement precision-based medicine, and optimize
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36 95 cerebral oxygenation to preserve neurological function.
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3 **98 Introduction:**
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6 **99** Medical advancements in the intensive care unit (ICU) has led to a substantial reduction in
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8 **100** mortality rates.^{1,2} However, survivors frequently experience post-intensive care syndrome
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10 **101** (PICS), which is characterized by cognitive, psychiatric, and physical impairments.³ These
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12 **102** complications have profound effects, including long-term cognitive impairments affecting
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14 **103** between 25-75% of survivors,³ and an approximately 50% decrease in full-time employment.⁴
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16 **104** Therefore, modern critical care research should improve our understanding of, and the
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18 **105** prevention of, long-term impairments in the growing number of ICU survivors.
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23 **106** A recent systematic review identified prolonged delirium as the most consistent and potentially
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25 **107** modifiable risk factor for long-term cognitive impairment.⁵ Patients with delirium experience
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27 **108** persistent deficits in various domains, including: memory, executive function, verbal fluency,
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29 **109** and attention.⁶⁻⁸ Furthermore, robotic technology known as the KINARM, which uses the
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31 **110** participant's upper limbs to assess sensorimotor and cognitive function, has indicated that ICU
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33 **111** survivors also develop visuospatial and motor deficits.⁹ Importantly, when assessed using the
34
35 **112** Repeatable Battery for Neuropsychological Status (RBANS), many critical illness survivors had
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37 **113** performance scores similar to patients with moderate traumatic brain injury or mild Alzheimer's
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39 **114** disease, with a duration-dependent effect of delirium on impairments in global cognition and
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41 **115** executive function.⁶
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46 **116** Delirium is characterized by reduced awareness, emotional disturbances, restlessness, and
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48 **117** incoherence with a 60-87% ICU incidence rate.¹⁰ While risk factors associated with delirium
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50 **118** include mechanical ventilation, age, and frailty,¹⁰ the underlying etiology of delirium is poorly
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52 **119** understood. Cerebral ischemia is thought to play a central role in delirium development;
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3 120 however, understanding this relationship presents several challenges due to the difficulty of
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5 121 continuously measuring cerebral perfusion in the ICU.
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8 122 This issue has resulted in a limited number of studies investigating the influence of cerebral
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10 123 perfusion on delirium in critically ill patients (Reviewed in¹¹). Near-infrared spectroscopy
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12 124 (NIRS) is a non-invasive technology that measures regional cerebral oxygenation (rSO₂) as a
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14 125 surrogate marker of cerebral perfusion,^{12,13} as rSO₂ values correlate with other markers of
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16 126 cerebral perfusion, including CT perfusion, jugular venous bulb oxygen saturation, and brain
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18 127 tissue oxygen tension.¹²⁻¹⁴ Therefore, NIRS is an ideal candidate for both ICU research and
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20 128 clinical practice.
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25 129 Feasibility and single-center prospective ICU studies have been performed with NIRS,
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27 130 discovering that low rSO₂ is an independent risk factor for the development of delirium.^{15,16} A
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29 131 nested cohort in this study demonstrated that impaired cerebral auto-regulation (i.e., the ability to
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31 132 maintain stabilized and adequate cerebral perfusion) is also associated with the development and
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33 133 duration of delirium.^{17,18} While these findings were statistically significant, a multi-centre
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35 134 observational study is necessary for external validation and the study of long-term outcomes.
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39 135 Our overarching hypothesis is that decreased rSO₂ in the early stages of critical illness leads to
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41 136 the development of delirium, as well as long-term cognitive impairment among survivors. The
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43 137 primary objective is to further establish an association between poor cerebral perfusion and
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45 138 delirium severity. Secondary objectives include assessing the hemodynamic and physiological
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47 139 determinants of rSO₂, as well as to identify potential risk factors (e.g., poor rSO₂) associated with
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49 140 delirium and long-term cognitive deficits. Overall, elucidating the mechanisms of acute and
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51 141 chronic neurological impairment will allow for the development of preventative treatments to
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53 142 improve outcomes among ICU survivors.
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3 **143 Methods and Analysis:**
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6 *144 Patient and Public Involvement:* At Kingston Health Sciences Centre (KHSC), our staff includes
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8 *145* a patient experience advisor who is a critical care nurse that has been previously admitted with
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10 *146* respiratory failure and shock. This experience as a front-line health care professional, as well as
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13 *147* an ICU patient, will be invaluable to both patient and public involvement. In addition to the
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15 *148* scientific community, patients and their families will also be central to the dissemination of our
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17 *149* findings. Participants that selected to be informed of the results will be mailed/e-mailed the
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20 *150* published findings upon study completion.
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23 *151 Study locations and participants:* An overall visual schematic of the study design is shown in
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25 *152* Figure 1. This prospective observational study will take place at 7 sites within Canada. KHSC
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27 *153* will serve as the coordinating centre, as the ICU has a history of coordinating academic and
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29 *154* industry funded studies and the staff are familiar with the CONFOCAL protocol, as the pilot
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31 *155* study¹⁶ was conducted at this site. Patients are considered eligible if they are ≥ 18 years old, have
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33 *156* been admitted to the ICU > 24 hours and have respiratory failure requiring invasive mechanical
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35 *157* ventilation with an expected duration > 24 hours, and/or have shock of any etiology. Shock will
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37 *158* be defined by the need for one of the following vasopressors/inotropes: Dopamine ≥ 7.5
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39 *159* mcg/kg/min, Dobutamine ≥ 5 mcg/kg/min, Norepinephrine ≥ 5 mcg/min, Phenylephrine ≥ 75
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41 *160* mcg/min, Epinephrine at any dose, Milrinone at any dose (if used in conjunction with another
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43 *161* agent), Vasopressin ≥ 0.03 u/min (if used in conjunction with another agent), which is adapted
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45 *162* from the BRAIN-ICU inclusion criteria.⁶ The exclusion criteria are admission to the ICU > 24
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47 *163* hours, a life expectancy < 24 hours, a primary central nervous system admitting diagnosis (e.g.,
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49 *164* traumatic brain injury, stroke, subarachnoid haemorrhage), and/or any reason that the subject
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51 *165* may not be able to participate in the follow up assessments (e.g., limb amputation, paresis,
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3 166 neuromuscular disorders). Post-cardiac arrest patients are also excluded from this study.
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5 167 Additional study sites will include the following: Toronto Western Hospital (Site PI Dr. Victoria
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7 168 McCredie), Université de Montreal (Montreal, QC; Site PI Dr. Michael Chasse), London Health
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10 169 Sciences Centre-Victoria Hospital (London, ON; Site PI Dr. Ian Ball, with co-PIs Dr. Marat
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12 170 Slesserev and Dr. Niamh O'Reagan), Ottawa General Hospital (Site PI Dr. Shane English),
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14 171 Ottawa Civic Hospital (Site PI Dr. Shane English), and Vancouver General Hospital (Site PI Dr.
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16 172 Donald Griesdale). KHSC is responsible for developing and maintaining the electronic case
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18 173 report forms (eCRF), data management, and analysis.
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24 175 *Recruitment and consent:* The Queen's University and Affiliated Hospitals Health Sciences
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26 176 Research Ethics Board will serve as the board of record for the streamlined research ethics
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28 177 review system (Clinical Trials Ontario) and all Ontario sites have gained approval; Non-Ontario
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30 178 sites will need to obtain local ethics approval at their earliest convenience. All patients admitted
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32 179 to the ICU will be screened daily for eligibility. The participant will be approached by a member
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34 180 of the research staff. If the participant is unable to provide consent, the research staff will
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36 181 approach the Substitute Decision Maker (SDM). The research coordinator or trained study staff
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38 182 will obtain informed consent and documentation of the consent process will be noted in the
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40 183 patient's medical chart. As patients meeting eligibility criteria are unlikely to be able to give
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42 184 informed consent at the time of enrolment due to their critical condition, we will employ a
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44 185 deferred consent model when appropriate (e.g., SDMs are frequently in an emotional state and
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46 186 may not be available to be contacted), which has already been granted local research ethics board
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48 187 approval. When an SDM is not available to approach, we will enrol the patient and begin trial
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52 188 procedures until the SDM is available for a consent encounter, targeted to be within 72 hours of
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3 189 enrolment. However, we will encourage an *a priori* informed consent whenever possible. The
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5 190 SDM response will be used to continue all trial procedures or any further data collection. If the
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8 191 patient or substitute decision maker declines enrolment, then the patient will be excluded, and all
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10 192 data obtained using deferred consent will be confidentially destroyed. In addition, once the
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12 193 patient has regained capacity according to the medical team, the patient will be approached to
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14 194 affirm or withdraw consent. Each site will be provided with patient identification numbers,
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16 195 which will be assigned sequentially when a patient is enrolled and will be used in all study
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18 196 documentation to ensure patient confidentiality and anonymity. All eligible patients will be
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20 197 recorded on a screening log, which will include their study ID, date of consent, or reason the
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22 198 patient could not be enrolled. The de-identified screening log will be forwarded to the lead
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24 199 project coordinator on a monthly basis. The individual site research coordinators and
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26 200 investigators will be responsible for ensuring the ethical conduct of this trial, screening patients,
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28 201 obtaining consent, and training of staff as needed. The principal investigators and co-
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30 202 investigators will review monthly compliance with the study protocol and recruitment rates.
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36 203 *Confidentiality:* To ensure patient confidentiality, identifying information will not be collected
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38 204 on the Case Report Form. Patients will be identified to the coordinating centre only by their
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40 205 unique study identification number. The site study coordinator will maintain a participant master
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42 206 list including the participant name and linked study ID. At the end of the study, this master list
43
44 207 will be destroyed. In accordance with current requirements, we will store the de-identified data
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46 208 for a minimum of 10 years.
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51 **Data Collection:**
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53 210 *rSO₂, hemodynamics, medications, and clinical characteristics:* Patients will be enrolled within
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55 211 the first 24 hours of their ICU admission. Immediately following enrolment, the patient will
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3 212 undergo rSO₂ monitoring. A sensor will be placed in the centre of the patient's forehead, which
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5 213 is attached to the FORESIGHT ELITE oximeter (CASMED, Caster Medical, Canada). This
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7
8 214 device will provide continuous quantification of rSO₂, every 2 seconds, for 72 hours. To assess
9
10 215 the association between hemodynamics and rSO₂ recordings, we will use a commercially
11
12 216 available system (Bedmaster, Excel Medical Electronics, FL, USA; or site equivalent) to capture
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14
15 217 the following vital signs from enrolled patients: heart rate (HR), systolic blood pressure (SBP),
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17 218 diastolic blood pressure (DBP), mean arterial pressure (MAP), and peripheral oxygen saturation
18
19 219 (SpO₂). These data are captured locally and uploaded to the eCRF (REDCap). Throughout this
20
21 220 72-hour period of recording, we will document administered continuous infusion and intermittent
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23 221 bolus doses of vasoactive and sedative/analgesic medications, which will be converted to either
24
25 222 "fentanyl equivalents" for narcotics, or "midazolam equivalents" for benzodiazepine
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28 223 medications. These conversion formulas have been previously described.¹⁹ Severity of illness
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30 224 will be measured during the first 24 hours of ICU admission using the Acute Physiology and
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32 225 Chronic Health Evaluation II score (APACHE II). Trained research staff will approach
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34 226 whomever provided informed consent (i.e., either the patient or the SDM) to ascertain the
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37 227 enrolled patient's pre-existing frailty (i.e., prior to ICU admission) using the clinical frailty
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39 228 scale,²⁰ which is 9-point scale (e.g., 1 = very fit to 9 = terminally ill). All clinical data will be
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42 229 captured on the eCRF.

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45 230 *Central venous and arterial blood collection:* Both arterial and central venous gases will be
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47 231 sampled every 12 hours during the 72h period of rSO₂ recording and will include: pH, partial
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49 232 pressure of oxygen (pO₂), partial pressure of carbon dioxide (pCO₂), and hemoglobin
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51 233 concentration (Hb). These blood samples will be collected only if a central line (PICC, internal
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53 234 jugular, subclavian) and arterial line are *already* in place.

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3 235 *Delirium screening:* Patients will be assessed once daily for delirium throughout their entire
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5 236 hospital stay (ICU and ward; up to day 30) using validated screening tools; the Confusion
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7 237 Assessment Method (CAM)-ICU²¹, as well as the brief Confusion Assessment Method
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9 238 (bCAM)²² which will be administered on the ward. Both delirium screening tools will be
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11 239 administered by trained research staff at a time that is convenient for the patient, their family,
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13 240 and the medical team directing their care.
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17 241 From the CAM-ICU, the CAM-ICU 7 (i.e., 7-point delirium severity scale) will also be
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19 242 documented (i.e., 0-2: no delirium, 3-5: mild to moderate delirium, and 6-7: severe delirium).²³
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21 243 The ICU discharge day will be considered to be the day that the attending writes orders to
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23 244 discharge, in order to avoid the influence of delayed discharge.
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27 245 *Determination of pre-existing cognitive impairment:* Our pilot study¹⁶ excluded 10% of patients
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29 246 with a documented history of cognitive impairment in their medical chart, which may limit
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31 247 external validity. Importantly, individuals may have substantial cognitive impairment prior to
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33 248 enrolment but did not receive any formal diagnosis. To address this potential confound, all
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35 249 patients will be assessed, upon enrolment, using the clinical dementia rating (CDR) scale.²⁴ The
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37 250 CDR is a scale from 0 (Normal) to 3 (severe dementia) that is calculated from a standardized
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39 251 scoring sheet completed by interviewing a patient or their caregiver. All staff completing the
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41 252 interview and scoring sheet will undergo rigorous online training and pass a certification exam.
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43 253 A diagnosis of pre-existing cognitive impairment will be defined as a CDR >1.
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52 **3- and 12-Month Follow Up:**
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3 256 *Neuropsychological assessment: Repeatable Battery for the Assessment of Neuropsychological*
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5 257 *Status (RBANS):* Participants will complete a 3- and 12-month follow up assessment in which
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7 258 the RBANS will be administered by a trained researcher. The RBANS assesses global cognition,
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9 259 as well as several subdomains (i.e., immediate and delayed memory, visuospatial/constructional,
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11 260 language, and attention). These indices have been described previously,²⁵ and survivors will be
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13 261 compared to age-matched controls. To improve follow up rates, in home/hospital testing will be
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15 262 performed for individuals not able to return for laboratory assessment. Participant scores are
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17 263 converted to standardized values in which the normative range will be considered a mean of
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19 264 100+/-24.75 (1.65 SD). Participants that score >75 will not be considered impaired, as these
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21 265 subjects are performing within or above the normative range. The RBANS assessment requires
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23 266 ~20-30 minutes to complete.

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29 267 *KINARM Assessment:* Participants (from the Kingston region only) will complete a 3- and 12-
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31 268 month follow up assessment using the End-Point bimanual KINARM robot (BKIN
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33 269 Technologies, Kingston). With each hand, the seated subject grasps a handle attached to a planar
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35 270 robotic device that permits movements in the horizontal plane with an integrated virtual reality
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37 271 system that presents objects in the horizontal plane (Figure 2). Subjects will perform a
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39 272 behavioural battery to quantify a broad range of sensorimotor, and cognitive function using their
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41 273 upper limbs. A trained operator selects a task from the software menu, reads the standardized
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43 274 instructions, and then monitors performance in real-time. We will administer 8 tasks from the
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45 275 KINARM Standard Tests™ including: Object Hit (OH),²⁶ Object Hit and Avoid (OHA),²⁷ Ball
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47 276 on Bar (BonB),²⁸ Visually Guided Reaching (VGR),²⁹ Reverse Visually Guided Reaching
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49 277 (RVGR),³⁰ Spatial Span (SS), Trail Making A and B, and Arm Position Matching (APM),³¹.
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51 278 Each task has been previously described,³² and quantifies subject performance using

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3 279 approximately 6 to 12 metrics per task. Each metric is converted into normalized units based on
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5 280 healthy subject performance, considering the influence of sex, age, and handedness (0 is mean
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7 281 performance and ± 1 is a standard deviation from the mean). For each task, a task score will also
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9 282 be generated to provide a global performance measure with values that are equivalent to standard
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11 283 deviation units with zero specifying best possible performance, and higher values indicating
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13 284 worse performance. Therefore, performance will be considered abnormal if the task score is
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15 285 outside the $+1.96$ range (i.e., 5th percentile). The task score has been previously described.³³ The
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17 286 KINARM assessment takes ~45 minutes to complete.
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25 288 **Statistical Plan:**

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28 289 *Quantification of disturbed cerebral autoregulation:* Cerebral autoregulation will be evaluated
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30 290 by computing customized algorithms (MATLAB, MathWorks, MA, USA) of the time-varying
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32 291 Spearman correlation coefficients between rSO_2 and MAP (i.e., cerebral autoregulation index,
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34 292 COx) with a moving time window advanced in 1 min steps over the 72-hour period of recording.
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36 293 This cerebral autoregulation assessment has been previously described¹⁸ and a visual
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38 294 representation can be observed in Figure 3. In addition, we will perform the COx across varying
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40 295 window lengths to further assess the optimal window length of recording (e.g., 5, 10, 30, 60, 120,
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42 296 240, 300-minute windows). Positive COx values (i.e., MAP and rSO_2 move in the same
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44 297 direction) reflect dysfunctional cerebral autoregulation, whereas negative (i.e., MAP and rSO_2
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46 298 move in the opposite direction) and near zero (< 0.3) indicate intact cerebral autoregulation.
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48 299 However, we will define cerebral autoregulation dysfunction by using a statistical significance
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50 300 threshold for positive COx correlation values ($p < 0.0001$). Cumulative duration of disturbed
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52 301 autoregulation will be given by the duration of time spent with a significant positive correlation
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3 302 throughout the period of neuromonitoring. Computer algorithms for COx will be developed and
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5 303 implemented blind to the neurological status of enrolled patients.
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8 304 *Estimating optimal MAP:* To calculate the individualized optimal MAP (MAP_{OPT}), the computed
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10 305 COx values will be binned by the average MAP value in their respective moving windows in 5
11
12 306 mmHg bins.³⁴ An alternative strategy will also be implemented. We will invert the MAP_{OPT}
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14 307 binning procedure by binning MAP values by their corresponding COx values in sequential 0.05
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16 308 bins of Spearman correlation coefficients ranging from -1 to +1. This procedure has been
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18 309 previously described.¹⁸
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23 310 *Assessment of primary outcome:* Multivariate linear regression will be used to characterize the
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25 311 association between adequate cerebral perfusion (as measured using duration of time (minutes)
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27 312 outside of MAP_{OPT} , mean rSO_2 , and duration of disturbed cerebral autoregulation) and delirium
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29 313 severity throughout a patient's ICU stay to determine if poor cerebral oxygenation is an
30
31 314 independent predictor of delirium. We will estimate the unadjusted effect of each individual
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33 315 predictor on delirium severity (i.e., cumulative CAM-7 scores per patient). The simultaneous
34
35 316 multivariate regression model will adjust for the following covariates due to their potential
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37 317 associations with delirium: a history of hypertension, a history of alcohol abuse, total sedative
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39 318 dose (in midazolam equivalents), total narcotic dose (in fentanyl equivalents), severity of illness
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41 319 (APACHE II scores), pre-existing cognitive impairment (CDR score), length of ICU stay, frailty,
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43 320 (clinical frailty scale) and blood urea nitrogen. The multivariable model will provide the adjusted
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45 321 regression coefficients after controlling for all predictors included in the model. All covariates
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47 322 included in regression modeling have been chosen *a priori* based on clinical judgment and
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49 323 previous research.^{16,35} Model diagnostics will be conducted to assess the underlying assumptions
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51 324 of linear regression (i.e., linearity, normally distributed residuals, equal variances, and lack of
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3 325 multicollinearity) for all models. Multiple imputation strategies will be applied at the time of the
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5 326 regression modeling to account for any missing data and reduce bias associated with excluding
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8 327 patients due to partially collected data.
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11 328 *Secondary outcomes:*

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14 329 *Determinants of rSO₂:* To assess the hemodynamic and physiological determinants of rSO₂ at the
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16 330 patient level, multiple linear regression will be performed using the patient average of each
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18 331 variable over the 72-hour data collection period. The following predictors will be included in the
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20 332 regression model: HR, SpO₂, MAP, arterial, and venous blood gas data (i.e., pH, pO₂, and
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22 333 pCO₂), central venous oxygen saturation, and Hb concentration. In addition, the multivariate
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24 334 model will control for the following covariates associated with cerebral perfusion: age,³⁶ as well
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26 335 as total sedative, narcotic, and vasopressor dosing. Simultaneous multiple linear regression with
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28 336 adjustment for all aforementioned covariates will be implemented. As stated for the primary
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30 337 outcome regression analysis, model diagnostics will be performed. Furthermore, the relationship
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32 338 between the determinants of the NIRS-derived rSO₂ signal may vary over time (see Figure 4 and
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34 339 Supplemental Movie 1). Therefore, a repeated measures analysis will also be performed by using
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36 340 multilevel modeling with 6 observations reflecting each 12-hour period during the 72-hour data
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38 341 collection period (with time coded as 0 – 5, so the intercept equals baseline/time of enrolment)
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40 342 nested within each subject. The predictors will be the same as the regression model but allowed
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42 343 to be time varying across the 6 observation points. This analysis will assess if within patient
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44 344 changes in the predictors correlate with changes in rSO₂, and if these associations are modified
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46 345 by fixed patient characteristics, such as age.
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53 346 *Assessing if poor cerebral perfusion during critical illness is a significant predictor of long-term*
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55 347 *neurological dysfunction among ICU survivors:* Multiple linear regression analysis will be used
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3 348 to assess if impaired cerebral perfusion (i.e., time below MAP_{OPT} , mean rSO_2 , and duration of
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5 349 disturbed cerebral autoregulation) is associated with RBANS global cognition scores at 3- and
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8 350 12-months post-ICU discharge. We will use the following clinical covariates collected on
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10 351 admission (i.e., pre-existing cognitive impairment, age, severity of illness, frailty) and data
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12 352 collected within the first 72 hours of the patients' ICU stay (i.e., narcotic dosing and
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14 353 benzodiazepine dosing). All covariates will be adjusted for in separate regression models for the
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16 354 cognitive outcomes at 3- and 12-months post-ICU discharge. If global cognition is significantly
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18 355 predicted by the time below MAP_{OPT} , we will conduct an exploratory analysis of the RBANS
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20 356 subdomains of cognition (i.e., delay and immediate memory, language, attention,
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22 357 visuospatial/constructional) adjusting for the aforementioned covariates to further explore
23
24 358 specific areas of impairment observed among survivors of critical illness. Due to the limited
25
26 359 availability of the KINARM robot across sites, only patients assessed at KHSC will undergo
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28 360 KINARM testing. This data will be assessed with descriptive statistics only to avoid any potential
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30 361 bias introduced by this design.

362 **Sample Size Calculation:**

363 *Primary Outcome:* Our overall hypothesis is that poor cerebral perfusion contributes to delirium
364 and long-term cognitive impairment. For study purposes, we define poor cerebral perfusion as
365 the composite of 1) low mean rSO_2 , 2) duration of impaired cerebral autoregulation, and 3) time
366 outside individualized optimal MAP (MAP_{OPT}), which will be discussed in more detail in the
367 statistical plan section. We acknowledge that this is an imperfect measure of cerebral perfusion.
368 However, this is a comprehensive, continuous, and non-invasive assessment of cerebral
369 perfusion. For our primary outcome (CAM-7 delirium severity score), we will enrol a total of
370 500 patients, as our prior work has demonstrated that ~20% of patients remain comatose (RASS

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3 371 = -4 or -5) during their entire ICU stay¹⁶, and cannot be assessed for delirium. Therefore, using
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5 372 our pilot data, we estimate that ~100 patients will be remain comatose resulting in approximately
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7 373 400 patients to assess our primary outcome, which will allow for 10 degrees of freedom for our 3
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9 374 measures of perfusion (i.e., mean rSO₂, duration of disturbed cerebral autoregulation, duration
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11 375 outside MAP_{OPT}) and controlling for the 9 covariates (see below). The 10 degrees of freedom
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13 376 will allow us to model non-linear relationships between the 3 measures of cerebral perfusion and
14
15 377 delirium severity. This sample size achieves 90% power to detect an R² of 0.050 collectively
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17 378 among these measures of cerebral perfusion and using an F-test with a significance level (alpha)
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19 379 of 0.050 (see Figure 5).
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24 380 *Secondary Outcomes-Physiological determinants of rSO₂ and neurological outcomes*

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27 381 For evaluating the determinants of the rSO₂ signal during critical illness, we will assess the
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29 382 association between each of the 9 pre-specified candidate predictors of rSO₂ after controlling for
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31 383 the 4 co-variates (see below for co-variates). We will use a Bonferroni correction
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33 384 (0.05/9=0.0056) to control for multiple testing. With the total 500 patients recruited, and a
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35 385 multivariate regression model that includes 13 independent variables, this testing strategy will
36
37 386 provide 90% power to identify any predictor that explains an additional 3.2% of the variance of
38
39 387 rSO₂ after controlling for the other variables in the model. This sample size is sufficient to
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41 388 identify independent significant predictors that account for a small-moderate degree of variance
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43 389 in the overall rSO₂ signal. However, our pilot data indicated a 30% mortality rate. Given our
44
45 390 overall sample size of 500 patients recruited, we are anticipating ~350 ICU survivors (i.e., 500-
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47 391 150) to return for follow up assessment. This cohort will provide sufficient power to detect
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49 392 important predictors of long-term neurological outcomes. However, these predictors have been
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3 393 intentionally not specified *a priori*, as this analysis will be dependent on our findings related to
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5 394 cerebral perfusion and delirium.
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8 395 All sample size calculations were conducted using Power Analysis and Sample Size Software
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10 396 (Version 15).³⁷
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16 398 The actual start date at KHSC began on January 26, 2018 and our estimated primary completion
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18 399 data is June 2022. Due to our 12 month follow up, we expect the study to be completed June
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20 400 2023.
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3 402 **DISCUSSION**
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6 403 This multicentre observational study will extend our preliminary findings of reduced rSO₂ as an
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8 404 independent risk factor for the development of delirium during critical illness. With the proposed
9
10 405 larger sample size, we will not only be able to replicate and validate this completely novel
11
12 406 finding, but we will also be able to further characterize the physiological determinants of rSO₂ in
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14 407 a representative cohort. Furthermore, this study will have the potential to identify novel
15
16 408 pathophysiological mechanism associated with the development of delirium and long-term
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18 409 neurological dysfunction among ICU survivors. These findings will inform the next phase of this
19
20 410 research program: a proof-of-principal study, aimed at devising strategies to optimize rSO₂. It
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22 411 will lay the foundation for a larger interventional study designed to assess whether optimization
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24 412 of rSO₂ can reduce delirium and improve long-term neurological outcomes for patients.
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3 415 **Ethics and Dissemination:**
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6 416 *Risks/Ethical Considerations:* Ethics approval will be obtained prior to the commencement of
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8 417 screening and enrolment at each site. There are no assumed risks associated with the proposed
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10 418 assessment procedures, as this study only involves a small amount of bloodwork, which will only
11
12 419 be collected if a central line and arterial line are *already* in place. Furthermore, results from our
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14 420 pilot study demonstrated that non-invasive monitoring of cerebral oxygenation, while using a
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16 421 deferred consent model, does not interfere with patient care or management.¹⁵ Research
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18 422 participants and their SDMs will be informed that enrolment in this study will not affect their
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20 423 care in any way, and that they have the right to refuse participation or withdraw at any time.
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25 424 *Dissemination of results:* The results of this study will be presented at national meetings of the
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27 425 Canadian Critical Care Trials Group. Prior to submitting any manuscript for publication, it will
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29 426 undergo rigorous internal peer review by this group of critical care experts. Our study group has
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31 427 a long track record of presenting our data at national and international critical care conferences.
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33 428 We anticipate the preliminary results of this research program will also be presented at these
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35 429 conferences (e.g., American Delirium Society). The final study results will be submitted for
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37 430 publication to high impact journals.
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15 **540 List of Abbreviations**
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17 541 APM: Arm Position Matching
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19 542 BonB: Ball on Bar
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21 543 bCAM: Brief Confusion Assessment Method
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23 544 CDR: Clinical Dementia Rating Scale
24

25 545 COx: Cerebral Oximetry Index
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27 546 Hb: Hemoglobin Concentration
28

29 547 HR: Heart Rate
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31 548 KHSC: Kingston Health Sciences Centre
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33 549 KINARM: Kinesiological Instrument for Normal and Altered Reaching Movement
34

35 550 ICU: Intensive Care Unit
36

37 551 MAP: Mean Arterial Pressure
38

39 552 MAP_{OPT}: Optimal Mean Arterial Pressure
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41 553 NIRS: Near-infrared Spectroscopy
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43 554 OH: Object Hit
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45 555 OHA: Object Hit and Avoid
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47 556 pCO₂: Arterial Partial Pressure of Carbon Dioxide
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49 557 PICS: Post-intensive Care Syndrome
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51 558 pO₂: Arterial Partial Pressure of Oxygen
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53 559 RASS: Richmond Agitation and Sedation Scale
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55 560 RBANS: Repeatable Battery for the Assessment of Neuropsychological Status
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57 561 rSO₂: Regional Cerebral Oxygenation
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3 562 RVGR: Reverse Visually Guided Reaching
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5 563 SpO₂: Peripheral Oxygen Saturation
6

7 564 SS: Spatial Span
8

9 565 SDM: Substitute Decision Maker
10

11 566 VGR: Visually Guided Reaching
12

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15 568 **Authors' contributions:**

16 569 MDW participated in study design, statistical planning, and drafting of the manuscript.
17

18 570 JK participated in study design and drafting of the manuscript.
19

20 571 KL participated in study design and drafting of the manuscript.
21

22 572 DM participated in study design and drafting of the manuscript.
23

24 573 JM participated in study design and drafting of the manuscript.
25

26 574 MH participated in study design and drafting of the manuscript.
27

28 575 SHS participated in study design and drafting of the manuscript.
29

30 576 AD participated in sample size calculations and finalizing of the statistical plan.
31

32 577 JAJ participated in statistical planning and drafting of the manuscript.
33

34 578 IB participated in study design and drafting of the manuscript.
35

36 579 MS participated in study design and drafting of the manuscript.
37

38 580 NO participated in study design and drafting of the manuscript.
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40 581 SE participated in study design and drafting of the manuscript.
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42 582 VM participated in study design and drafting of the manuscript.
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44 583 MC participated in study design and drafting of the manuscript.
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46 584 DG participated in study design and drafting of the manuscript.
47

48 585 JGB is the primary investigator. He participated in study design and drafting of the manuscript.
49

50 586
51

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4 591 analysis.

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6 592

7
8 **593 Competing interests statement.**

9
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11
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13
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15
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24
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3 **617 Figure Legends:**
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5 **618 Figure 1.** A visual representation of the CONFOCAL2 study design from enrolment to 3- and
6 **619** 12-month follow up assessments.
7

8 **620 Figure 2.** Three-dimensional animated representation of the KINARM End-Point robotic set-up
9 **621** used at 3- and 12-month follow up assessments.
10

11 **622 Figure 3A.** Simplified line graph (24 hours instead of the full 72 hour recording period)
12 **623** illustrating the sliding window correlation between mean arterial pressure and regional cerebral
13 **624** oxygenation for an individual patient over a 24 period of recording. *Note.* The black rectangle
14 **625** represents a 60-minute window that moves forward 1-minute at a time until the recording period
15 **626** is completed. **B.** Scatter plot illustrating a time dependent positive association between mean
16 **627** arterial pressure and regional cerebral oxygenation. *Note.* Black dots represent data collected for
17 **628** an individual patient over 24 hours, with the blue line representing a linear model fit to the data,
18 **629** and the grey shaded region representing the 95% confidence interval. **C.** Scatter plot indicating
19 **630** the time varying association between mean arterial pressure and regional cerebral oxygenation
20 **631** represented as the cerebral oximetry index (COx) over an individual patient's 24-hour recording
21 **632** period. *Note.* Statistically significant ($p < 0.0001$) positive Cox values represent dysfunctional
22 **633** cerebral autoregulation, with negative or near zero values indicating intact cerebral
23 **634** autoregulation.
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28 **635 Figure 4.** Line graph of the high frequency vital sign recordings indicates the highly variable
29 **636** relationships with regional cerebral oxygenation over the 72-hour period of recording. *Note.* The
30 **637** figure represents a single patient's ICU recording. rSO₂ = Regional cerebral oxygenation; HR =
31 **638** Heart rate; SpO₂ = Arterial oxygen saturation; artMAP= Mean arterial pressure from an arterial
32 **639** line.
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35 **640 Figure 5.** A power curve indicating the study sample size, and the respective statistical power, to
36 **641** assess the primary study outcome. *Note.* Red dots represent the sample size needed for a given
37 **642** statistical power. The primary sample size was calculated using the following multivariate
38 **643** regression model parameters: 10 independent variables tested, controlling for 9 additional
39 **644** covariates, power = 0.90, R² = 0.050, α = 0.05, which would require a sample size of 400.
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Inclusion Criteria

- >17 years old
- >24hr mechanical ventilation due to respiratory failure and/or shock

Exclusion Criteria

- Neurological/neurosurgical admitting diagnosis
- <24hr life expectancy
- Inability to participate in follow-up

Enrolment

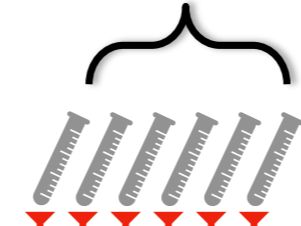
Covariates Collected

- Pre-existing cognitive dysfunction
- History of hypertension
- History of alcohol abuse
- Severity of Illness (APACHE II)
- Sedative + narcotic dose
- Blood urea nitrogen
- Length of ICU stay



Blood Samples

- pH
- pO2
- pCO2
- Hb conc.



0 hours

72 hours

30 days

3 months

12 months

Vitals

NIRS

Delirium

CAM-ICU (ICU)
bCAM (Ward)

+ Severity

RBANS

KINARM

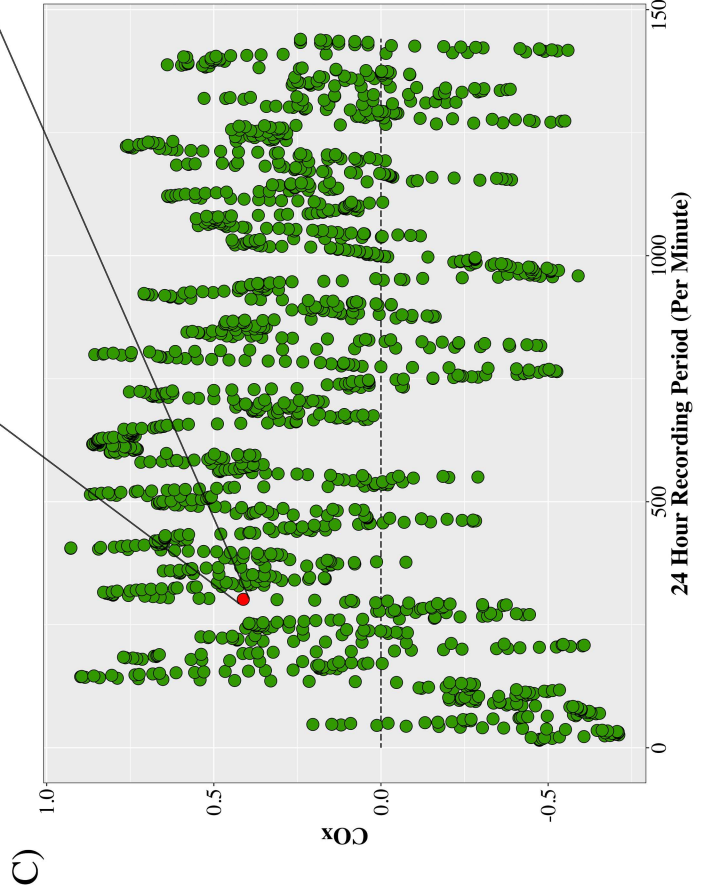
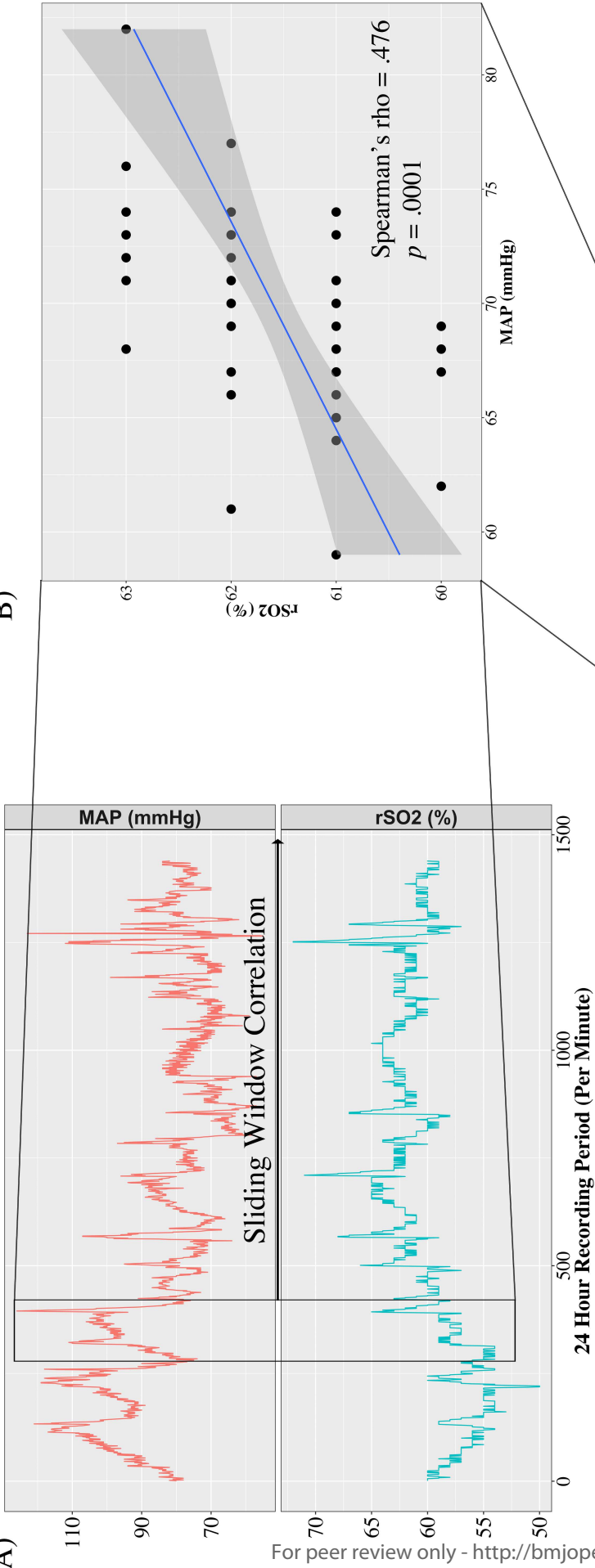
RBANS

KINARM

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Enrolment

24 Hours

48 Hours

72 Hours

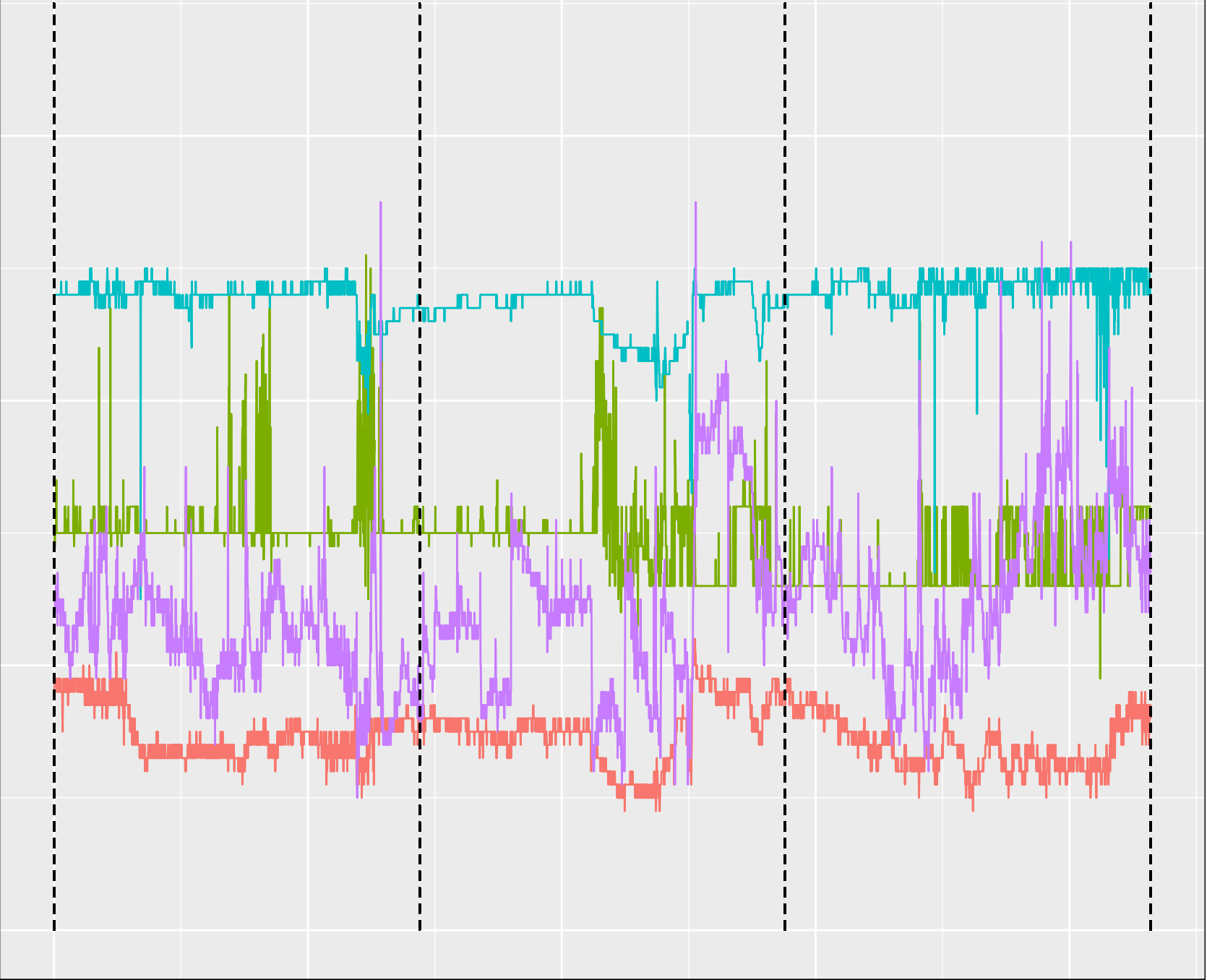
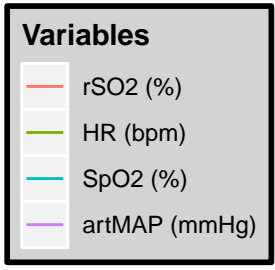
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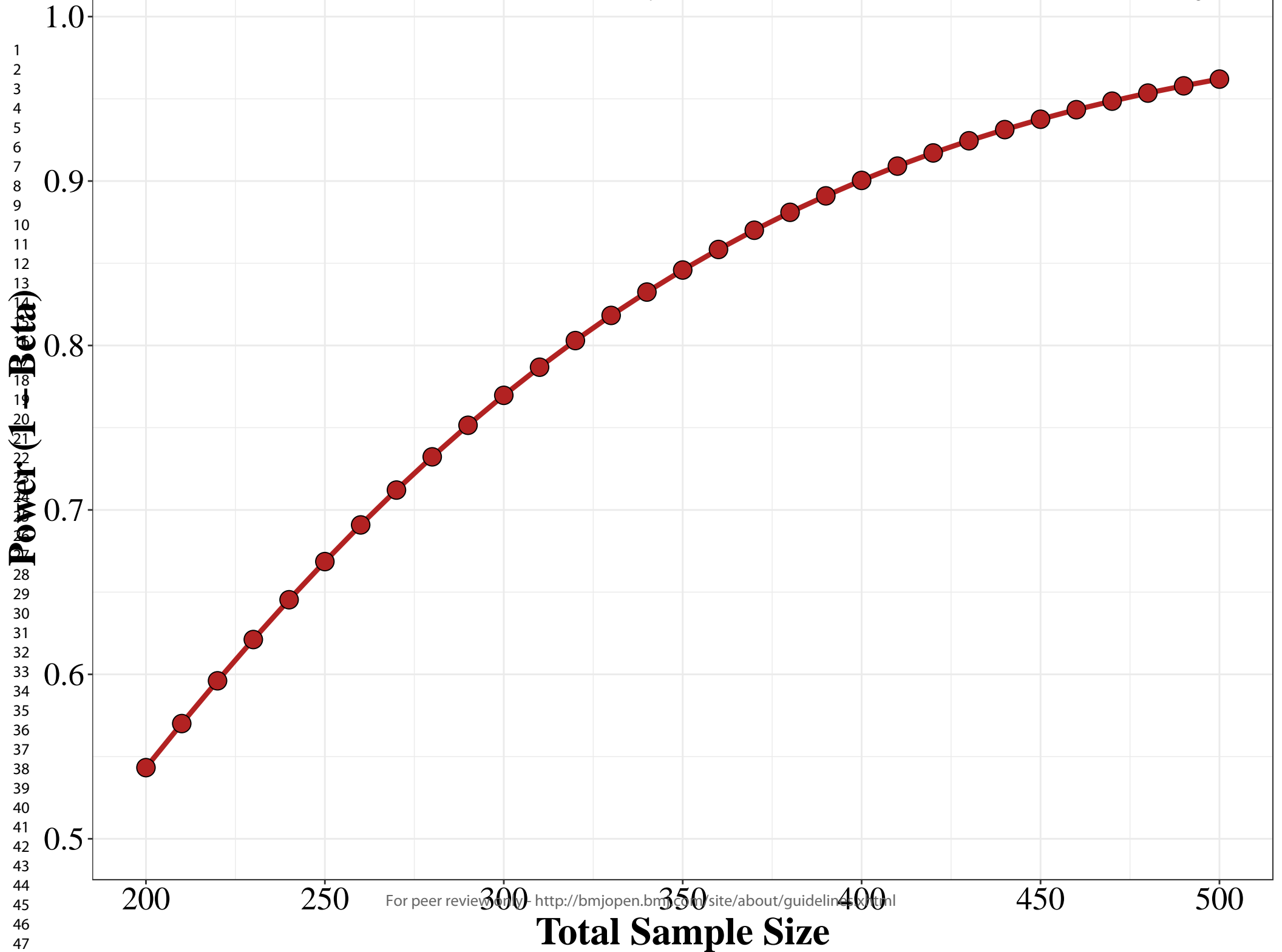
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72 Hour Recording Period (Per Minute)





STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page Number on which item is reported
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	25-26
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-2,25
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	25-26
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	9-10
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6-7
	6b	Explanation for choice of comparators	6-7
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	N/A
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	16-18

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10-13
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	14-15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	14-15
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	N/A
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			

1 2 3 4 5 6 7 8 9 10 11	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10-13
12 13 14 15 16 17		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	14-15
18 19 20 21 22 23 24 25	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8-10
26 27 28 29 30 31	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15-18
32 33 34		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15-18
35 36 37 38 39 40		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15-18
41 42	Methods: Monitoring			
43 44 45 46 47 48 49 50 51 52	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
53 54 55 56 57 58 59 60		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	20
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	9,20
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9-10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9-10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	26
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	10
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	20

	31b	Authorship eligibility guidelines and any intended use of professional writers	20
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	20
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)" license.

BMJ Open

Assessing the relationship between near-infrared spectroscopy derived regional cerebral oxygenation and neurological dysfunction in critically ill adults: a prospective observational multi-centre protocol, on behalf of the Canadian Critical Care Trials Group

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-029189.R2
Article Type:	Protocol
Date Submitted by the Author:	24-May-2019
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Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Neurology
Keywords:	Near-infrared spectroscopy, Cerebral autoregulation, KINARM, Delirium, Post-intensive care syndrome, RBANS

Note: The following files were submitted by the author for peer review, but cannot be converted to PDF. You must view these files (e.g. movies) online.

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Supplemental Figure 1.gif

SCHOLARONE™
Manuscripts

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5 2 Title: Assessing the relationship between near-infrared spectroscopy derived
6 3 regional cerebral oxygenation and neurological dysfunction in critically ill
7 4 adults: a prospective observational multi-centre protocol, on behalf of the
8 5 Canadian Critical Care Trials Group
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10 7

11 8 Authors: The Cerebral Oxygenation and Neurological Outcomes Following
12 9 Critical Illness (CONFOCAL) Research Group
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For peer review only

Abstract:

Introduction: Survivors of critical illness frequently exhibit acute and chronic neurological complications. The underlying etiology of this dysfunction remains unknown but may be associated with cerebral ischemia. This study will use near-infrared spectroscopy (NIRS) to non-invasively quantify regional cerebral oxygenation (rSO₂) to assess the association between poor rSO₂ during the first 72 hours of critical illness with delirium severity, as well as long-term sensorimotor and cognitive impairment among intensive care unit (ICU) survivors. Further, the physiological determinants of rSO₂ will be examined.

Methods and analysis: This multi-centre prospective observational study will consider adult patients (≥ 18 years old) eligible for enrolment if within 24 hours of ICU admission, they require mechanical ventilation, and/or vasopressor support. For 72 hours, rSO₂ will be continuously recorded, while vital signs (e.g., heart rate) and peripheral oxygenation saturation will be concurrently captured with data monitoring software. Arterial and central venous gases will be sampled every 12 hours for the 72h recording period and will include: pH, partial pressure of oxygen, partial pressure of carbon dioxide, and hemoglobin concentration. Participants will be screened daily for delirium with the confusion assessment method (CAM)-ICU, whereas the brief-CAM will be used on the ward. At 3- and 12-months post-ICU discharge, neurological function will be assessed with the Repeatable Battery for the Assessment of Neuropsychological Status and KINARM sensorimotor and cognitive robot-based behavioral tasks.

Ethics and Dissemination: The study protocol has been approved in Ontario by a central research ethics board (Clinical Trials Ontario); non-Ontario sites will obtain local ethics approval. The study will be conducted under the guidance of the Canadian Critical Care Trials Group (CCCTG) and the results of this study will be presented at national meetings of the CCCTG for internal

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3 72 peer review. Results will also be presented at national/international scientific conferences. Upon
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5 73 completion, the study findings will be submitted for publication in peer-reviewed journals.
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8 74 *Trial Registration:* This trial is registered on clinicaltrials.gov (Identifier: [NCT03141619](https://clinicaltrials.gov/ct2/show/study/NCT03141619)),
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10 75 registered May 5, 2017.
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13 76 *Key Words:* Near-infrared spectroscopy; Cerebral oximetry; Cerebral autoregulation; KINARM,
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15 77 Delirium; CAM-ICU; Post-intensive care syndrome; RBANS
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3 81 **Strengths and Limitations of this study:**
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- 6 82 • CONFOCAL2 will further assess the association between poor regional cerebral
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8 83 oxygenation (rSO₂) and delirium, as well as long-term cognitive outcomes among
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10 84 survivors.
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13 85 • Although this study is observational in nature, which limits causal inferences, broad
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15 86 inclusion criteria and a representative sample size will increase external validity of our
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17 87 findings.
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20 88 • CONFOCAL2 closely resembles routine clinical practice with only minor
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22 89 methodological differences (e.g., rSO₂ monitoring) and results will have the potential to
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24 90 directly translate into clinical practice.
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3 **93 Introduction:**
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6 94 Medical advancements in the intensive care unit (ICU) has led to a substantial reduction in
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8 95 mortality rates.^{1,2} However, survivors frequently experience post-intensive care syndrome
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10 96 (PICS), which is characterized by cognitive, psychiatric, and physical impairments.³ These
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12 97 complications have profound effects, including long-term cognitive impairments affecting
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14 98 between 25-75% of survivors,³ and an approximately 50% decrease in full-time employment.⁴
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16 99 Therefore, modern critical care research should improve our understanding of, and the
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18 100 prevention of, long-term impairments in the growing number of ICU survivors.
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23 101 A recent systematic review identified prolonged delirium as the most consistent and potentially
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25 102 modifiable risk factor for long-term cognitive impairment.⁵ Patients with delirium experience
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27 103 persistent deficits in various domains, including: memory, executive function, verbal fluency,
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29 104 and attention.⁶⁻⁸ Furthermore, robotic technology known as the KINARM, which uses the
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31 105 participant's upper limbs to assess sensorimotor and cognitive function, has indicated that ICU
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33 106 survivors also develop visuospatial and motor deficits.⁹ Importantly, when assessed using the
34
35 107 Repeatable Battery for Neuropsychological Status (RBANS), many critical illness survivors had
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37 108 performance scores similar to patients with moderate traumatic brain injury or mild Alzheimer's
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39 109 disease, with a duration-dependent effect of delirium on impairments in global cognition and
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41 110 executive function.⁶
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46 111 Delirium is characterized by reduced awareness, emotional disturbances, restlessness, and
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48 112 incoherence with a 60-87% ICU incidence rate.¹⁰ While risk factors associated with delirium
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50 113 include mechanical ventilation, age, and frailty,¹⁰ the underlying etiology of delirium is poorly
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52 114 understood. Cerebral ischemia is thought to play a central role in delirium development;
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3 115 however, understanding this relationship presents several challenges due to the difficulty of
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5 116 continuously measuring cerebral perfusion in the ICU.
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8 117 This issue has resulted in a limited number of studies investigating the influence of cerebral
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10 118 perfusion on delirium in critically ill patients (Reviewed in¹¹). Near-infrared spectroscopy
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12 119 (NIRS) is a non-invasive technology that measures regional cerebral oxygenation (rSO₂) as a
13
14 120 surrogate marker of cerebral perfusion,^{12,13} as rSO₂ values correlate with other markers of
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16 121 cerebral perfusion, including CT perfusion, jugular venous bulb oxygen saturation, and brain
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18 122 tissue oxygen tension.¹²⁻¹⁴ Therefore, NIRS is an ideal candidate for both ICU research and
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20 123 clinical practice.
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25 124 Feasibility and single-center prospective ICU studies have been performed with NIRS,
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27 125 discovering that low rSO₂ is an independent risk factor for the development of delirium.^{15,16} A
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29 126 nested cohort in this study demonstrated that impaired cerebral auto-regulation (i.e., the ability to
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31 127 maintain stabilized and adequate cerebral perfusion) is also associated with the development and
32
33 128 duration of delirium.^{17,18} While these findings were statistically significant, a multi-centre
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35 129 observational study is necessary for external validation and the study of long-term outcomes.
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40 130 Our overarching hypothesis is that decreased rSO₂ in the early stages of critical illness leads to
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42 131 the development of delirium, as well as long-term cognitive impairment among survivors. The
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44 132 primary objective is to further establish an association between poor cerebral perfusion and
45
46 133 delirium severity. Secondary objectives include assessing the hemodynamic and physiological
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48 134 determinants of rSO₂, as well as to identify potential risk factors (e.g., poor rSO₂) associated with
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50 135 delirium and long-term cognitive deficits. Overall, elucidating the mechanisms of acute and
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52 136 chronic neurological impairment will allow for the development of preventative treatments to
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55 137 improve outcomes among ICU survivors.
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3 **138 Methods and Analysis:**
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6 *139 Patient and Public Involvement:* At Kingston Health Sciences Centre (KHSC), our staff includes
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8 *140* a patient experience advisor who is a critical care nurse that has been previously admitted with
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10 *141* respiratory failure and shock. This experience as a front-line health care professional, as well as
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12 *142* an ICU patient, will be invaluable to both patient and public involvement. In addition to the
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14 *143* scientific community, patients and their families will also be central to the dissemination of our
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16 *144* findings. Participants that selected to be informed of the results will be mailed/e-mailed the
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18 *145* published findings upon study completion.
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23 *146 Study locations and participants:* An overall visual schematic of the study design is shown in
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25 *147* Figure 1. This prospective observational study will take place at 5 sites within Ontario, Canada.
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27 *148* KHSC will serve as the coordinating centre, as the ICU has a history of coordinating academic
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29 *149* and industry funded studies and the staff are familiar with the CONFOCAL protocol, as the pilot
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31 *150* study¹⁶ was conducted at this site. Patients are considered eligible if they are ≥ 18 years old, have
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33 *151* been admitted to the ICU > 24 hours and have respiratory failure requiring invasive mechanical
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35 *152* ventilation with an expected duration > 24 hours, and/or have shock of any etiology. Shock will
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37 *153* be defined by the need for one of the following vasopressors/inotropes: Dopamine ≥ 7.5
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39 *154* mcg/kg/min, Dobutamine ≥ 5 mcg/kg/min, Norepinephrine ≥ 5 mcg/min, Phenylephrine ≥ 75
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41 *155* mcg/min, Epinephrine at any dose, Milrinone at any dose (if used in conjunction with another
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43 *156* agent), Vasopressin ≥ 0.03 u/min (if used in conjunction with another agent), which is adapted
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45 *157* from the BRAIN-ICU inclusion criteria.⁶ The exclusion criteria are admission to the ICU > 24
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47 *158* hours, a life expectancy < 24 hours, a primary central nervous system admitting diagnosis (e.g.,
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49 *159* traumatic brain injury, stroke, subarachnoid haemorrhage), and/or any reason that the subject
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51 *160* may not be able to participate in the follow up assessments (e.g., limb amputation, paresis,
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3 161 neuromuscular disorders). Post-cardiac arrest patients are also excluded from this study.
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5 162 Additional study sites will include the following: London Health Sciences Centre-Victoria
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8 163 Hospital (London, ON; Site PI Dr. Ian Ball, with co-PIs Dr. Marat Slesserev and Dr. Niamh
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10 164 O'Reagan), Ottawa General Hospital (Site PI Dr. Shane English), and Ottawa Civic Hospital
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12 165 (Site PI Dr. Shane English). KHSC is responsible for developing and maintaining the electronic
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15 166 case report forms (eCRF), data management, and analysis.
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19 168 *Potential non-Ontario site expansion:* We are anticipating an enrolment rate of 1-2 patients per
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21 169 site/month. Should our enrolment rates be slower than anticipated, additional sites have already
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24 170 agreed to participate in this study, including: Toronto Western Hospital (Site PI Dr. Victoria
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26 171 McCredie, Université de Montreal (Montreal, QC; Site PI Dr. Michael Chasse) and Vancouver
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28 172 General Hospital (Site PI Dr. Donald Griesdale). Local Ethics approval would be sought prior to
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31 173 enrolment in this study.
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35 175 *Recruitment and consent:* The Queen's University and Affiliated Hospitals Health Sciences
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37 176 Research Ethics Board will serve as the board of record for the streamlined research ethics
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40 177 review system (Clinical Trials Ontario) and all Ontario sites have gained approval; Non-Ontario
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42 178 sites will need to obtain local ethics approval at their earliest convenience. All patients admitted
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45 179 to the ICU will be screened daily for eligibility. The participant will be approached by a member
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47 180 of the research staff. If the participant is unable to provide consent, the research staff will
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49 181 approach the Substitute Decision Maker (SDM). The research coordinator or trained study staff
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51 182 will obtain informed consent and documentation of the consent process will be noted in the
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54 183 patient's medical chart. As patients meeting eligibility criteria are unlikely to be able to give
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3 184 informed consent at the time of enrolment due to their critical condition, we will employ a
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5 185 deferred consent model when appropriate (e.g., SDMs are frequently in an emotional state and
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7 186 may not be available to be contacted), which has already been granted local research ethics board
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9 187 approval. When an SDM is not available to approach, we will enrol the patient and begin trial
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11 188 procedures until the SDM is available for a consent encounter, targeted to be within 72 hours of
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13 189 enrolment. However, we will encourage an *a priori* informed consent whenever possible. The
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15 190 SDM response will be used to continue all trial procedures or any further data collection. If the
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17 191 patient or substitute decision maker declines enrolment, then the patient will be excluded, and all
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19 192 data obtained using deferred consent will be confidentially destroyed. In addition, once the
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21 193 patient has regained capacity according to the medical team, the patient will be approached to
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23 194 affirm or withdraw consent. Each site will be provided with patient identification numbers,
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25 195 which will be assigned sequentially when a patient is enrolled and will be used in all study
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27 196 documentation to ensure patient confidentiality and anonymity. All eligible patients will be
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29 197 recorded on a screening log, which will include their study ID, date of consent, or reason the
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31 198 patient could not be enrolled. The de-identified screening log will be forwarded to the lead
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33 199 project coordinator on a monthly basis. The individual site research coordinators and
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35 200 investigators will be responsible for ensuring the ethical conduct of this trial, screening patients,
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37 201 obtaining consent, and training of staff as needed. The principal investigators and co-
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39 202 investigators will review monthly compliance with the study protocol and recruitment rates.

40 203 *Confidentiality:* To ensure patient confidentiality, identifying information will not be collected
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42 204 on the Case Report Form. Patients will be identified to the coordinating centre only by their
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44 205 unique study identification number. The site study coordinator will maintain a participant master
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46 206 list including the participant name and linked study ID. At the end of the study, this master list

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3 207 will be destroyed. In accordance with current requirements, we will store the de-identified data
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5 208 for a minimum of 10 years.
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8 **209 Data Collection:**
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11 210 *rSO₂, hemodynamics, medications, and clinical characteristics:* Patients will be enrolled within
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13 211 the first 24 hours of their ICU admission. Immediately following enrolment, the patient will
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15 212 undergo rSO₂ monitoring. A sensor will be placed in the centre of the patient's forehead, which
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17 213 is attached to the FORESIGHT ELITE oximeter (CASMED, Caster Medical, Canada). This
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19 214 device will provide continuous quantification of rSO₂, every 2 seconds, for 72 hours. To assess
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21 215 the association between hemodynamics and rSO₂ recordings, we will use a commercially
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23 216 available system (Bedmaster, Excel Medical Electronics, FL, USA; or site equivalent) to capture
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25 217 the following vital signs from enrolled patients: heart rate (HR), systolic blood pressure (SBP),
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27 218 diastolic blood pressure (DBP), mean arterial pressure (MAP), and peripheral oxygen saturation
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29 219 (SpO₂). These data are captured locally and uploaded to the eCRF (REDCap). Throughout this
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31 220 72-hour period of recording, we will document administered continuous infusion and intermittent
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33 221 bolus doses of vasoactive and sedative/analgesic medications, which will be converted to either
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35 222 "fentanyl equivalents" for narcotics, or "midazolam equivalents" for benzodiazepine
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37 223 medications. These conversion formulas have been previously described.¹⁹ Severity of illness
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39 224 will be measured during the first 24 hours of ICU admission using the Acute Physiology and
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41 225 Chronic Health Evaluation II score (APACHE II). Trained research staff will approach
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43 226 whomever provided informed consent (i.e., either the patient or the SDM) to ascertain the
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45 227 enrolled patient's pre-existing frailty (i.e., prior to ICU admission) using the clinical frailty
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47 228 scale,²⁰ which is 9-point scale (e.g., 1 = very fit to 9 = terminally ill). All clinical data will be
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49 229 captured on the eCRF.
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3 230 *Central venous and arterial blood collection:* Both arterial and central venous gases will be
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5 231 sampled every 12 hours during the 72h period of rSO₂ recording and will include: pH, partial
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7 232 pressure of oxygen (pO₂), partial pressure of carbon dioxide (pCO₂), and hemoglobin
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9 233 concentration (Hb). These blood samples will be collected only if a central line (PICC, internal
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11 234 jugular, subclavian) and arterial line are *already* in place.

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15 235 *Delirium screening:* Patients will be assessed once daily for delirium throughout their entire
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17 236 hospital stay (ICU and ward; up to day 30) using validated screening tools; the Confusion
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19 237 Assessment Method (CAM)-ICU²¹, as well as the brief Confusion Assessment Method
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21 238 (bCAM)²² which will be administered on the ward. Both delirium screening tools will be
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23 239 administered by trained research staff at a time that is convenient for the patient, their family,
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25 240 and the medical team directing their care.

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30 241 From the CAM-ICU, the CAM-ICU 7 (i.e., 7-point delirium severity scale) will also be
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32 242 documented (i.e., 0-2: no delirium, 3-5: mild to moderate delirium, and 6-7: severe delirium).²³
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34 243 The ICU discharge day will be considered to be the day that the attending writes orders to
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36 244 discharge, in order to avoid the influence of delayed discharge.

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40 245 *Determination of pre-existing cognitive impairment:* Our pilot study¹⁶ excluded 10% of patients
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42 246 with a documented history of cognitive impairment in their medical chart, which may limit
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44 247 external validity. Importantly, individuals may have substantial cognitive impairment prior to
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46 248 enrolment but did not receive any formal diagnosis. To address this potential confound, all
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48 249 patients will be assessed, upon enrolment, using the clinical dementia rating (CDR) scale.²⁴ The
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50 250 CDR is a scale from 0 (Normal) to 3 (severe dementia) that is calculated from a standardized
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52 251 scoring sheet completed by interviewing a patient or their caregiver. All staff completing the
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3 252 interview and scoring sheet will undergo rigorous online training and pass a certification exam.
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5 253 A diagnosis of pre-existing cognitive impairment will be defined as a CDR >1.
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11 **3- and 12-Month Follow Up:**
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14 256 *Neuropsychological assessment: Repeatable Battery for the Assessment of Neuropsychological*
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17 257 *Status (RBANS):* Participants will complete a 3- and 12-month follow up assessment in which
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19 258 the RBANS will be administered by a trained researcher. The RBANS assesses global cognition,
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21 259 as well as several subdomains (i.e., immediate and delayed memory, visuospatial/constructional,
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23 260 language, and attention). These indices have been described previously,²⁵ and survivors will be
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25 261 compared to age-matched controls. To improve follow up rates, in home/hospital testing will be
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27 262 performed for individuals not able to return for laboratory assessment. Participant scores are
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29 263 converted to standardized values in which the normative range will be considered a mean of
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31 264 100+/-24.75 (1.65 SD). Participants that score >75 will not be considered impaired, as these
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33 265 subjects are performing within or above the normative range. The RBANS assessment requires
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35 266 ~20-30 minutes to complete.
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40 267 *KINARM Assessment:* Participants (from the Kingston region only) will complete a 3- and 12-
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42 268 month follow up assessment using the End-Point bimanual KINARM robot (BKIN
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44 269 Technologies, Kingston). With each hand, the seated subject grasps a handle attached to a planar
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46 270 robotic device that permits movements in the horizontal plane with an integrated virtual reality
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48 271 system that presents objects in the horizontal plane (Figure 2). Subjects will perform a
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50 272 behavioural battery to quantify a broad range of sensorimotor, and cognitive function using their
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52 273 upper limbs. A trained operator selects a task from the software menu, reads the standardized
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3 274 instructions, and then monitors performance in real-time. We will administer 8 tasks from the
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5 275 KINARM Standard Tests™ including: Object Hit (OH),²⁶ Object Hit and Avoid (OHA),²⁷ Ball
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8 276 on Bar (BonB),²⁸ Visually Guided Reaching (VGR),²⁹ Reverse Visually Guided Reaching
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10 277 (RVGR),³⁰ Spatial Span (SS), Trail Making A and B, and Arm Position Matching (APM),³¹.
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12 278 Each task has been previously described,³²and quantifies subject performance using
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14 279 approximately 6 to 12 metrics per task. Each metric is converted into normalized units based on
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16 280 healthy subject performance, considering the influence of sex, age, and handedness (0 is mean
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18 281 performance and ± 1 is a standard deviation from the mean). For each task, a task score will also
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20 282 be generated to provide a global performance measure with values that are equivalent to standard
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22 283 deviation units with zero specifying best possible performance, and higher values indicating
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24 284 worse performance. Therefore, performance will be considered abnormal if the task score is
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26 285 outside the +1.96 range (i.e., 5th percentile). The task score has been previously described.³³ The
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31 286 KINARM assessment takes ~45 minutes to complete.

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35 36 37 288 **Statistical Plan:**

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39 289 *Quantification of disturbed cerebral autoregulation:* Cerebral autoregulation will be evaluated
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41 290 by computing customized algorithms (MATLAB, MathWorks, MA, USA) of the time-varying
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43 291 Spearman correlation coefficients between rSO₂ and MAP (i.e., cerebral autoregulation index,
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45 292 COx) with a moving time window advanced in 1 min steps over the 72-hour period of recording.
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47 293 This cerebral autoregulation assessment has been previously described¹⁸ and a visual
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49 294 representation can be observed in Figure 3. In addition, we will perform the COx across varying
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51 295 window lengths to further assess the optimal window length of recording (e.g., 5, 10, 30, 60, 120,
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53 296 240, 300-minute windows). Positive COx values (i.e., MAP and rSO₂ move in the same
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3 297 direction) reflect dysfunctional cerebral autoregulation, whereas negative (i.e., MAP and rSO₂
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5 298 move in the opposite direction) and near zero (< 0.3) indicate intact cerebral autoregulation.
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8 299 However, we will define cerebral autoregulation dysfunction by using a statistical significance
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10 300 threshold for positive COx correlation values (p<0.0001). Cumulative duration of disturbed
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12 301 autoregulation will be given by the duration of time spent with a significant positive correlation
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14 302 throughout the period of neuromonitoring. Computer algorithms for COx will be developed and
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16 303 implemented blind to the neurological status of enrolled patients.
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20 304 *Estimating optimal MAP:* To calculate the individualized optimal MAP (MAP_{OPT}), the computed
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22 305 COx values will be binned by the average MAP value in their respective moving windows in 5
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24 306 mmHg bins.³⁴ An alternative strategy will also be implemented. We will invert the MAP_{OPT}
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26 307 binning procedure by binning MAP values by their corresponding COx values in sequential 0.05
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28 308 bins of Spearman correlation coefficients ranging from -1 to +1. This procedure has been
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30 309 previously described.¹⁸
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34 310 *Assessment of primary outcome:* Multivariate linear regression will be used to characterize the
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36 311 association between adequate cerebral perfusion (as measured using duration of time (minutes)
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38 312 outside of MAP_{OPT}, mean rSO₂, and duration of disturbed cerebral autoregulation) and delirium
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40 313 severity throughout a patient's ICU stay to determine if poor cerebral oxygenation is an
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42 314 independent predictor of delirium. We will estimate the unadjusted effect of each individual
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44 315 predictor on delirium severity (i.e., cumulative CAM-7 scores per patient). The simultaneous
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46 316 multivariate regression model will adjust for the following covariates due to their potential
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48 317 associations with delirium: a history of hypertension, a history of alcohol abuse, total sedative
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50 318 dose (in midazolam equivalents), total narcotic dose (in fentanyl equivalents), severity of illness
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52 319 (APACHE II scores), pre-existing cognitive impairment (CDR score), length of ICU stay, frailty,
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3 320 (clinical frailty scale) and blood urea nitrogen. The multivariable model will provide the adjusted
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5 321 regression coefficients after controlling for all predictors included in the model. All covariates
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7 322 included in regression modeling have been chosen *a priori* based on clinical judgment and
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9
10 323 previous research.^{16,35} Model diagnostics will be conducted to assess the underlying assumptions
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12 324 of linear regression (i.e., linearity, normally distributed residuals, equal variances, and lack of
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14 325 multicollinearity) for all models. Multiple imputation strategies will be applied at the time of the
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16 326 regression modeling to account for any missing data and reduce bias associated with excluding
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19 327 patients due to partially collected data.
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22 328 *Secondary outcomes:*
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25 329 *Determinants of rSO₂:* To assess the hemodynamic and physiological determinants of rSO₂ at the
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27 330 patient level, multiple linear regression will be performed using the patient average of each
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29 331 variable over the 72-hour data collection period. The following predictors will be included in the
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31 332 regression model: HR, SpO₂, MAP, arterial, and venous blood gas data (i.e., pH, pO₂, and
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33 333 pCO₂), central venous oxygen saturation, and Hb concentration. In addition, the multivariate
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35 334 model will control for the following covariates associated with cerebral perfusion: age,³⁶ as well
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37 335 as total sedative, narcotic, and vasopressor dosing. Simultaneous multiple linear regression with
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39 336 adjustment for all aforementioned covariates will be implemented. As stated for the primary
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41 337 outcome regression analysis, model diagnostics will be performed. Furthermore, the relationship
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43 338 between the determinants of the NIRS-derived rSO₂ signal may vary over time (see Figure 4 and
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45 339 Supplemental Movie 1). Therefore, a repeated measures analysis will also be performed by using
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47 340 multilevel modeling with 6 observations reflecting each 12-hour period during the 72-hour data
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49 341 collection period (with time coded as 0 – 5, so the intercept equals baseline/time of enrolment)
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51 342 nested within each subject. The predictors will be the same as the regression model but allowed
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3 343 to be time varying across the 6 observation points. This analysis will assess if within patient
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5 344 changes in the predictors correlate with changes in rSO₂, and if these associations are modified
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8 345 by fixed patient characteristics, such as age.
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10 346 *Assessing if poor cerebral perfusion during critical illness is a significant predictor of long-term*
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13 347 *neurological dysfunction among ICU survivors:* Multiple linear regression analysis will be used
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15 348 to assess if impaired cerebral perfusion (i.e., time below MAP_{OPT}, mean rSO₂, and duration of
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17 349 disturbed cerebral autoregulation) is associated with RBANS global cognition scores at 3- and
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20 350 12-months post-ICU discharge. We will use the following clinical covariates collected on
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22 351 admission (i.e., pre-existing cognitive impairment, age, severity of illness, frailty) and data
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24 352 collected within the first 72 hours of the patients' ICU stay (i.e., narcotic dosing and
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26 353 benzodiazepine dosing). All covariates will be adjusted for in separate regression models for the
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28 354 cognitive outcomes at 3- and 12-months post-ICU discharge. If global cognition is significantly
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30 355 predicted by the time below MAP_{OPT}, we will conduct an exploratory analysis of the RBANS
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32 356 subdomains of cognition (i.e., delay and immediate memory, language, attention,
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34 357 visuospatial/constructional) adjusting for the aforementioned covariates to further explore
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36 358 specific areas of impairment observed among survivors of critical illness. Due to the limited
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38 359 availability of the KINARM robot across sites, only patients assessed at KHSC will undergo
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40 360 KINARM testing. This data will be assessed with descriptive statistics only to avoid any potential
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43 361 bias introduced by this design.
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48 362 **Sample Size Calculation:**

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51 363 *Primary Outcome:* Our overall hypothesis is that poor cerebral perfusion contributes to delirium
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53 364 and long-term cognitive impairment. For study purposes, we define poor cerebral perfusion as
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55 365 the composite of 1) low mean rSO₂, 2) duration of impaired cerebral autoregulation, and 3) time
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3 366 outside individualized optimal MAP (MAP_{OPT}), which will be discussed in more detail in the
4
5 367 statistical plan section. We acknowledge that this is an imperfect measure of cerebral perfusion.
6
7 368 However, this is a comprehensive, continuous, and non-invasive assessment of cerebral
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9 369 perfusion. For our primary outcome (CAM-7 delirium severity score), we will enrol a total of
10
11 370 500 patients, as our prior work has demonstrated that ~20% of patients remain comatose (RASS
12
13 371 = -4 or -5) during their entire ICU stay¹⁶, and cannot be assessed for delirium. Therefore, using
14
15 372 our pilot data, we estimate that ~100 patients will remain comatose resulting in approximately
16
17 373 400 patients to assess our primary outcome, which will allow for 10 degrees of freedom for our 3
18
19 374 measures of perfusion (i.e., mean rSO_2 , duration of disturbed cerebral autoregulation, duration
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21 375 outside MAP_{OPT}) and controlling for the 9 covariates (see below). The 10 degrees of freedom
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23 376 will allow us to model non-linear relationships between the 3 measures of cerebral perfusion and
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25 377 delirium severity. This sample size achieves 90% power to detect an R^2 of 0.050 collectively
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27 378 among these measures of cerebral perfusion and using an F-test with a significance level (α)
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29 379 of 0.050 (see Figure 5).
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36 380 *Secondary Outcomes-Physiological determinants of rSO_2 and neurological outcomes*

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39 381 For evaluating the determinants of the rSO_2 signal during critical illness, we will assess the
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41 382 association between each of the 9 pre-specified candidate predictors of rSO_2 after controlling for
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43 383 the 4 co-variates (see below for co-variates). We will use a Bonferroni correction
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45 384 ($0.05/9=0.0056$) to control for multiple testing. With the total 500 patients recruited, and a
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47 385 multivariate regression model that includes 13 independent variables, this testing strategy will
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49 386 provide 90% power to identify any predictor that explains an additional 3.2% of the variance of
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51 387 rSO_2 after controlling for the other variables in the model. This sample size is sufficient to
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53 388 identify independent significant predictors that account for a small-moderate degree of variance
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3 389 in the overall rSO₂ signal. However, our pilot data indicated a 30% mortality rate. Given our
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5 390 overall sample size of 500 patients recruited, we are anticipating ~350 ICU survivors (i.e., 500-
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7 391 150) to return for follow up assessment. This cohort will provide sufficient power to detect
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9 392 important predictors of long-term neurological outcomes. However, these predictors have been
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11 393 intentionally not specified *a priori*, as this analysis will be dependent on our findings related to
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13 394 cerebral perfusion and delirium.
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17 395 All sample size calculations were conducted using Power Analysis and Sample Size Software
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19 396 (Version 15).³⁷
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25 398 The actual start date at KHSC began on January 26, 2018 and our estimated primary completion
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27 399 data is June 2022. Due to our 12 month follow up, we expect the study to be completed June
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29 400 2023.
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3 402 **DISCUSSION**
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6 403 This multicentre observational study will extend our preliminary findings of reduced rSO₂ as an
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8 404 independent risk factor for the development of delirium during critical illness. With the proposed
9
10 405 larger sample size, we will not only be able to replicate and validate this completely novel
11
12 406 finding, but we will also be able to further characterize the physiological determinants of rSO₂ in
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14 407 a representative cohort. Furthermore, this study will have the potential to identify novel
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16 408 pathophysiological mechanism associated with the development of delirium and long-term
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18 409 neurological dysfunction among ICU survivors. These findings will inform the next phase of this
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20 410 research program: a proof-of-principal study, aimed at devising strategies to optimize rSO₂. It
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22 411 will lay the foundation for a larger interventional study designed to assess whether optimization
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24 412 of rSO₂ can reduce delirium and improve long-term neurological outcomes for patients.
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3 415 **Ethics and Dissemination:**
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6 416 *Risks/Ethical Considerations:* Ethics approval will be obtained prior to the commencement of
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8 417 screening and enrolment at each site. There are no assumed risks associated with the proposed
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10 418 assessment procedures, as this study only involves a small amount of bloodwork, which will only
11
12 419 be collected if a central line and arterial line are *already* in place. Furthermore, results from our
13
14 420 pilot study demonstrated that non-invasive monitoring of cerebral oxygenation, while using a
15
16 421 deferred consent model, does not interfere with patient care or management.¹⁵ Research
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18 422 participants and their SDMs will be informed that enrolment in this study will not affect their
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20 423 care in any way, and that they have the right to refuse participation or withdraw at any time.
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25 424 *Dissemination of results:* The results of this study will be presented at national meetings of the
26
27 425 Canadian Critical Care Trials Group. Prior to submitting any manuscript for publication, it will
28
29 426 undergo rigorous internal peer review by this group of critical care experts. Our study group has
30
31 427 a long track record of presenting our data at national and international critical care conferences.
32
33 428 We anticipate the preliminary results of this research program will also be presented at these
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35 429 conferences (e.g., American Delirium Society). The final study results will be submitted for
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37 430 publication to high impact journals.
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4

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11
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15 **540 List of Abbreviations**
16

17 541 APM: Arm Position Matching
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19 542 BonB: Ball on Bar
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21 543 bCAM: Brief Confusion Assessment Method
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23 544 CDR: Clinical Dementia Rating Scale
24

25 545 COx: Cerebral Oximetry Index
26

27 546 Hb: Hemoglobin Concentration
28

29 547 HR: Heart Rate
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31 548 KHSC: Kingston Health Sciences Centre
32

33 549 KINARM: Kinesiological Instrument for Normal and Altered Reaching Movement
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35 550 ICU: Intensive Care Unit
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37 551 MAP: Mean Arterial Pressure
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39 552 MAP_{OPT}: Optimal Mean Arterial Pressure
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41 553 NIRS: Near-infrared Spectroscopy
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43 554 OH: Object Hit
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45 555 OHA: Object Hit and Avoid
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47 556 pCO₂: Arterial Partial Pressure of Carbon Dioxide
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49 557 PICS: Post-intensive Care Syndrome
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51 558 pO₂: Arterial Partial Pressure of Oxygen
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53 559 RASS: Richmond Agitation and Sedation Scale
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55 560 RBANS: Repeatable Battery for the Assessment of Neuropsychological Status
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57 561 rSO₂: Regional Cerebral Oxygenation
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3 562 RVGR: Reverse Visually Guided Reaching
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5 563 SpO₂: Peripheral Oxygen Saturation
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7 564 SS: Spatial Span
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9 565 SDM: Substitute Decision Maker
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11 566 VGR: Visually Guided Reaching
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15 568 **Authors' contributions:**

16 569 MDW participated in study design, statistical planning, and drafting of the manuscript.
17

18 570 JK participated in study design and drafting of the manuscript.
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20 571 KL participated in study design and drafting of the manuscript.
21

22 572 DM participated in study design and drafting of the manuscript.
23

24 573 JM participated in study design and drafting of the manuscript.
25

26 574 MH participated in study design and drafting of the manuscript.
27

28 575 SHS participated in study design and drafting of the manuscript.
29

30 576 AD participated in sample size calculations and finalizing of the statistical plan.
31

32 577 JAJ participated in statistical planning and drafting of the manuscript.
33

34 578 IB participated in study design and drafting of the manuscript.
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36 579 MS participated in study design and drafting of the manuscript.
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38 580 NO participated in study design and drafting of the manuscript.
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40 581 SE participated in study design and drafting of the manuscript.
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42 582 VM participated in study design and drafting of the manuscript.
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44 583 MC participated in study design and drafting of the manuscript.
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46 584 DG participated in study design and drafting of the manuscript.
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48 585 JGB is the primary investigator. He participated in study design and drafting of the manuscript.
49

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51

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54

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3 590 recipient. The funding agencies had no role in the design of this study, data collection, or data
4 591 analysis.

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7
8 **593 Competing interests statement.**

9
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11
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13
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15
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17
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24
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26
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46 615 as a Regional Medical Lead.

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3 617 **Figure Legends:**
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5 618 **Figure 1.** A visual representation of the CONFOCAL2 study design from enrolment to 3- and
6 619 12-month follow up assessments.

8 620 **Figure 2.** Three-dimensional animated representation of the KINARM End-Point robotic set-up
9 621 used at 3- and 12-month follow up assessments.

11 622 **Figure 3A.** Simplified line graph (24 hours instead of the full 72 hour recording period)
12 623 illustrating the sliding window correlation between mean arterial pressure and regional cerebral
13 624 oxygenation for an individual patient over a 24 period of recording. *Note.* The black rectangle
14 625 represents a 60-minute window that moves forward 1-minute at a time until the recording period
15 626 is completed. **B.** Scatter plot illustrating a time dependent positive association between mean
16 627 arterial pressure and regional cerebral oxygenation. *Note.* Black dots represent data collected for
17 628 an individual patient over 24 hours, with the blue line representing a linear model fit to the data,
18 629 and the grey shaded region representing the 95% confidence interval. **C.** Scatter plot indicating
19 630 the time varying association between mean arterial pressure and regional cerebral oxygenation
20 631 represented as the cerebral oximetry index (COx) over an individual patient's 24-hour recording
21 632 period. *Note.* Statistically significant ($p < 0.0001$) positive Cox values represent dysfunctional
22 633 cerebral autoregulation, with negative or near zero values indicating intact cerebral
23 634 autoregulation.

28 635 **Figure 4.** Line graph of the high frequency vital sign recordings indicates the highly variable
29 636 relationships with regional cerebral oxygenation over the 72-hour period of recording. *Note.* The
30 637 figure represents a single patient's ICU recording. rSO₂ = Regional cerebral oxygenation; HR =
31 638 Heart rate; SpO₂ = Arterial oxygen saturation; artMAP= Mean arterial pressure from an arterial
32 639 line.

35 640 **Figure 5.** A power curve indicating the study sample size, and the respective statistical power, to
36 641 assess the primary study outcome. *Note.* Red dots represent the sample size needed for a given
37 642 statistical power. The primary sample size was calculated using the following multivariate
38 643 regression model parameters: 10 independent variables tested, controlling for 9 additional
39 644 covariates, power = 0.90, R² = 0.050, α = 0.05, which would require a sample size of 400.

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Inclusion Criteria

- >17 years old
- >24hr mechanical ventilation due to respiratory failure and/or shock

Exclusion Criteria

- Neurological/neurosurgical admitting diagnosis
- <24hr life expectancy
- Inability to participate in follow-up

Enrolment

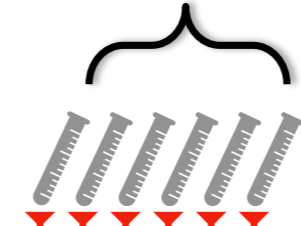
Covariates Collected

- Pre-existing cognitive dysfunction
- History of hypertension
- History of alcohol abuse
- Severity of Illness (APACHE II)
- Sedative + narcotic dose
- Blood urea nitrogen
- Length of ICU stay



Blood Samples

- pH
- pO2
- pCO2
- Hb conc.



Vitals

NIRS

Delirium

CAM-ICU (ICU)
bCAM (Ward)

+ Severity

RBANS

KINARM

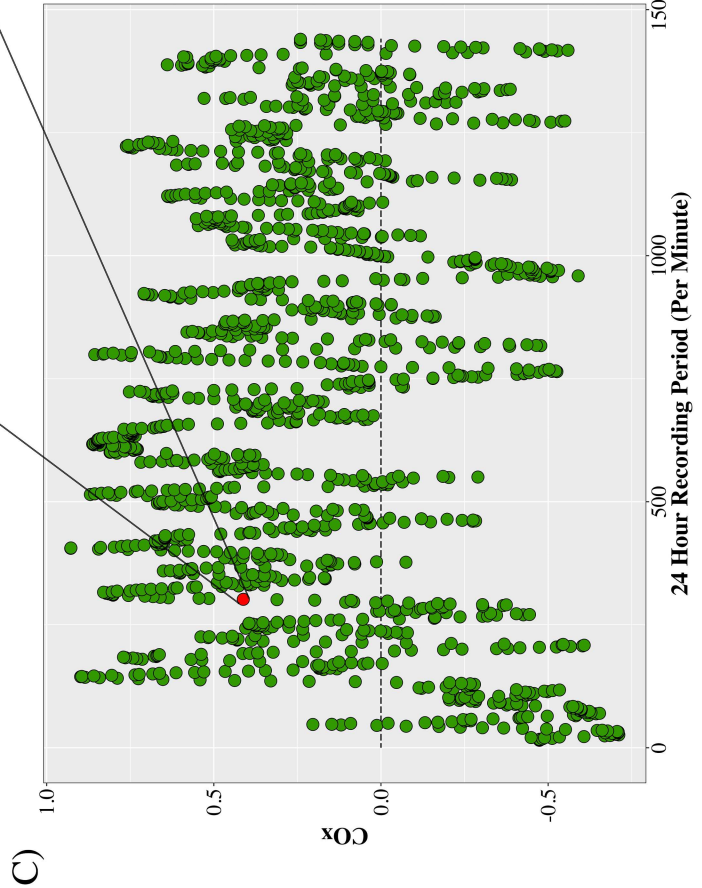
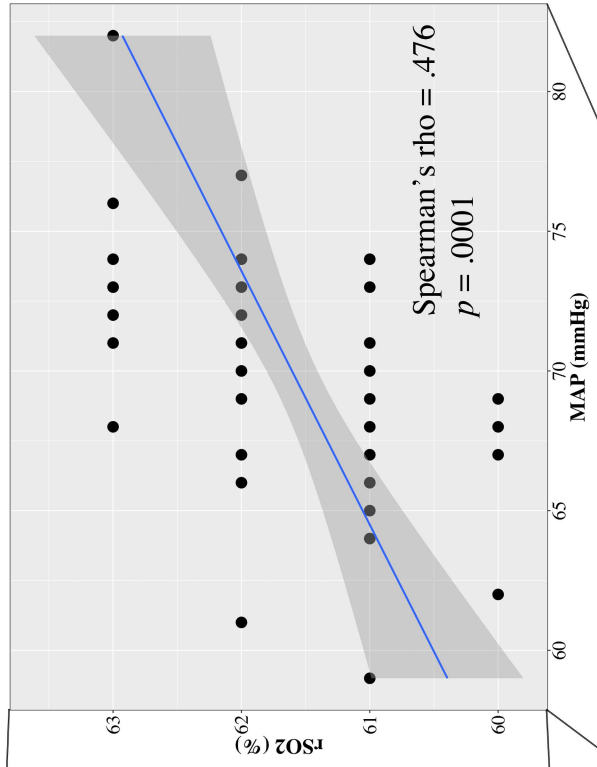
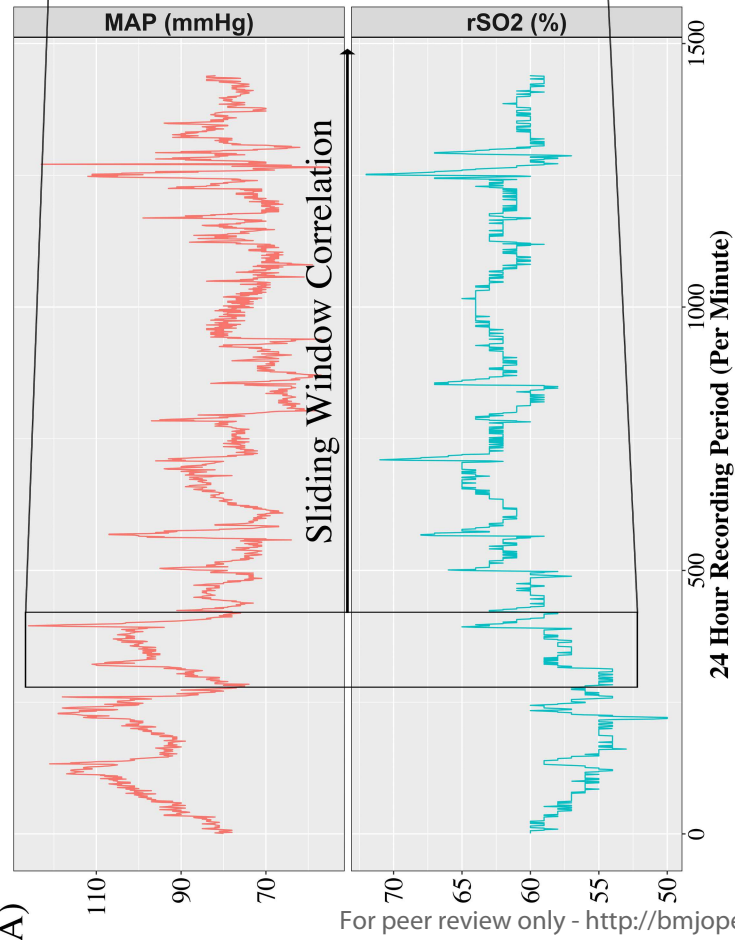
RBANS

KINARM

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Enrolment

24 Hours

48 Hours

72 Hours

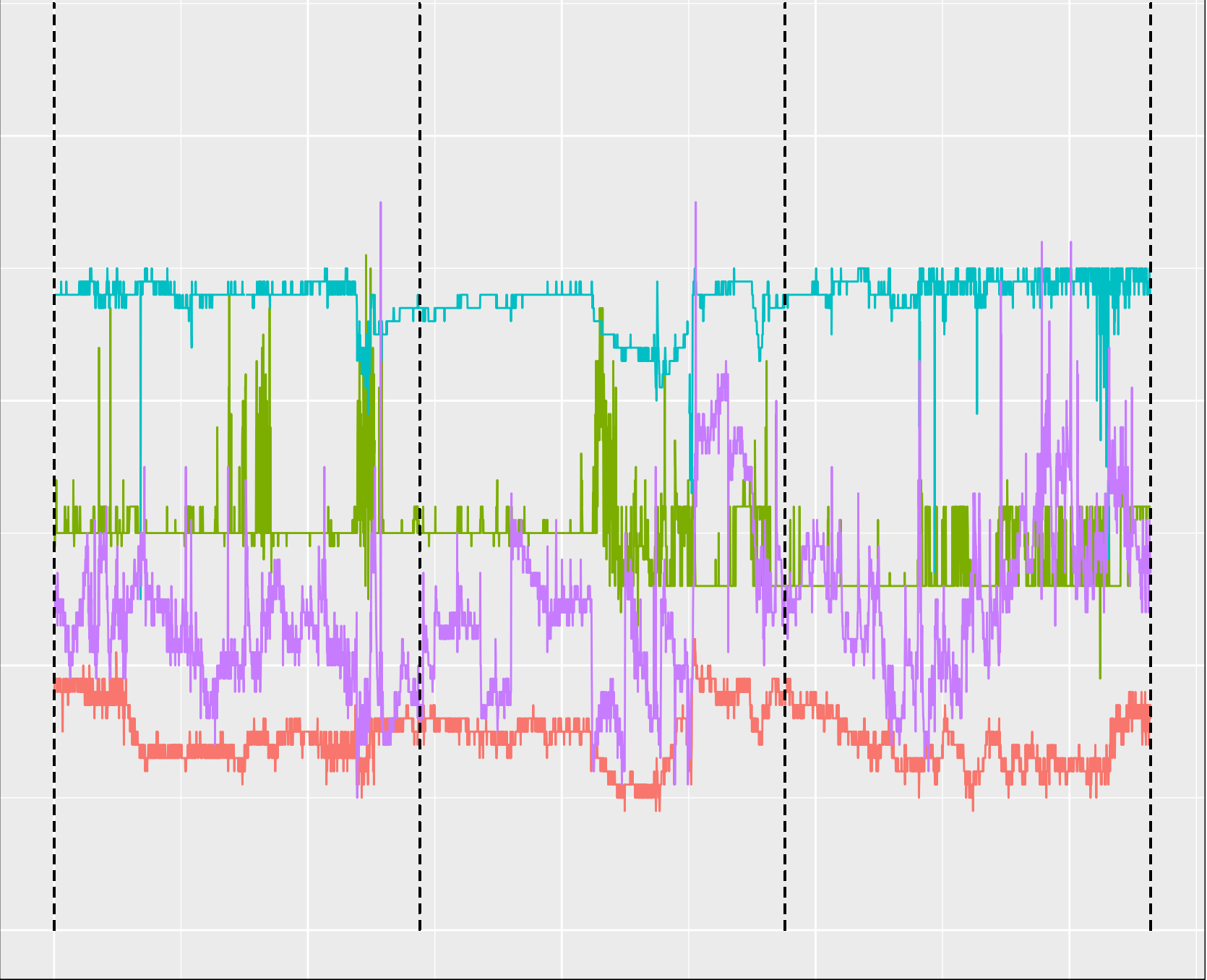
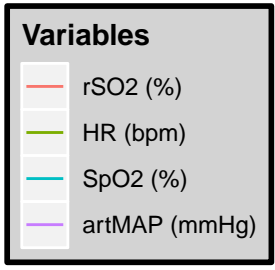
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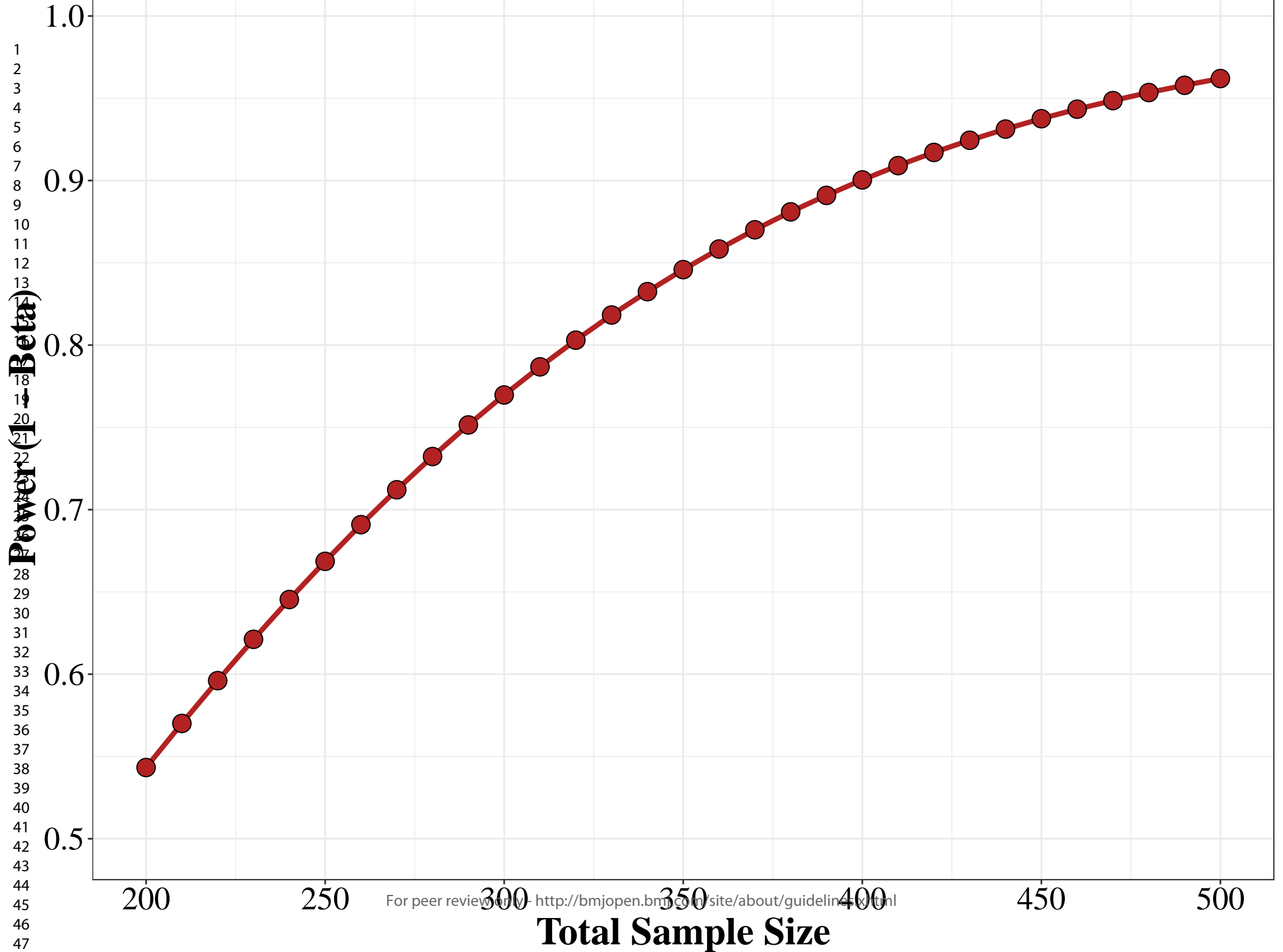
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72 Hour Recording Period (Per Minute)





STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page Number on which item is reported
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	25-26
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-2,25
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	25-26
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	9-10
Introduction			

1 2 3 4 5 6	Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6-7
7 8		6b	Explanation for choice of comparators	6-7
9 10	Objectives	7	Specific objectives or hypotheses	7
11 12 13 14 15 16	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
17	Methods: Participants, interventions, and outcomes			
18 19 20 21 22 23 24	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
25 26 27 28 29 30	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	N/A
		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
49 50 51 52 53 54 55 56 57 58 59 60	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	16-18

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10-13
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	14-15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	14-15
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	N/A
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			

1 2 3 4 5 6 7 8 9 10 11	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10-13
12 13 14 15 16 17		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	14-15
18 19 20 21 22 23 24 25	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8-10
26 27 28 29 30 31	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15-18
32 33 34		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15-18
35 36 37 38 39 40		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15-18
41 42	Methods: Monitoring			
43 44 45 46 47 48 49 50 51 52	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
53 54 55 56 57 58 59 60		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	20
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	9,20
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9-10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9-10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	26
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	10
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	20

	31b	Authorship eligibility guidelines and any intended use of professional writers	20
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	20
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)" license.