BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-029189
Article Type:	Protocol
Date Submitted by the Author:	17-Jan-2019
Keywords:	Near-infrared spectroscopy, Cerebral autoregulation, KINARM, Delirium, Post-intensive care syndrome, RBANS

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Supplemental Figure 1.gif

Title: 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

Authors: The Cerebral Oxygenation and Neurological Outcomes Following Critical Illness (CONFOCAL) Research Group

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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 (rSO_2) to assess the association between poor rSO_2 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, rSO_2 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

peer review. Results will also be presented at national/international scientific conferences. Upon completion, the study findings will be submitted for publication in peer-reviewed journals.

Trial Registration: This trial is registered on clinicaltrials.gov (Identifier: NCT03141619), registered May 5, 2017.

Key Words: Near-infrared spectroscopy; Cerebral oximetry; Cerebral autoregulation; KINARM, Delirium; CAM-ICU; Post-intensive care syndrome; RBANS

Strengths and Limitations of this study:

- Potential to replicate our previous finding that poor regional cerebral oxygenation (rSO_2) 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 rSO_2 monitoring.
- Further assessment of dysfunctional cerebral autoregulation as a potential underlying mechanism associated with poor rSO_2 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 rSO_2 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.

This issue has resulted in a limited number of studies investigating the influence of cerebral perfusion on delirium in critically ill patients (Reviewed in[11]). Near-infrared spectroscopy (NIRS) is a non-invasive technology that measures regional cerebral oxygenation (rSO_2) as a surrogate marker of cerebral perfusion,[12,13] as rSO_2 values correlate with other markers of cerebral perfusion, including CT perfusion, jugular venous bulb oxygen saturation, and brain tissue oxygen tension.[12–14] Therefore, NIRS is an ideal candidate for both ICU research and clinical practice.

Feasibility and single-center prospective ICU studies have been performed with NIRS, discovering that low rSO_2 is an independent risk factor for the development of delirium.[15,16] A nested cohort in this study demonstrated that impaired cerebral auto-regulation (i.e., the ability to maintain stabilized and adequate cerebral perfusion) is also associated with the development and duration of delirium.[17,18] While these findings were statistically significant, a multi-centre observational study is necessary for external validation and the study of long-term outcomes.

Our overarching hypothesis is that decreased rSO_2 in the early stages of critical illness leads to the development of delirium, as well as long-term cognitive impairment among survivors. The study objectives are to further establish an association between rSO_2 and delirium, and to identify potential risk factors associated with delirium and long-term cognitive deficits. Overall, elucidating the mechanisms of delirium will allow for the development of preventative 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 study[16] 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,

neuromuscular disorders). Post-cardiac arrest patients are also excluded from this study. Additional study sites will include the following: Toronto Western Hospital (Site PI Dr. Victoria McCredie), Université de Montreal (Montreal, QC; Site PI Dr. Michael Chasse), Victoria Hospital (London, ON; Site PI Dr. Ian Ball, with co-PIs Dr. Marat Slesserev and Dr. Niamh O'Reagan), Ottawa General Hospital (Site PI Dr. Shane English), Ottawa Civic Hospital (Site PI Dr. Shane English), and Vancouver General Hospital (Site PI Dr. Donald Griesdale). KHSC is responsible for developing and maintaining the electronic case report forms (eCRF), data management, and analysis. Recruitment at KHSC began on January 17, 2018.

Recruitment and consent: The Queen's University and Affiliated Hospitals Health Sciences Research Ethics Board will serve as the board of record for the streamlined research ethics review system (Clinical Trials Ontario) for which KHSC has gained approval; Non-Ontario sites will obtain local ethics approval. All patients admitted to the ICU will be screened daily for eligibility. The participant will be approached by a member of the research staff. If the participant is unable to provide consent, the research staff will approach the Substitute Decision Maker (SDM). The research coordinator or trained study staff will obtain informed consent and documentation of the consent process will be noted in the patient's medical chart. As patients meeting eligibility criteria are unlikely to be able to give informed consent at the time of enrolment due to their critical condition, we will employ a deferred consent model when appropriate (e.g., SDMs are frequently in an emotional state and may not be available to be contacted), which has already been granted local research ethics board approval. When an SDM is not available to approach, we will enrol the patient and begin trial procedures until the SDM is available for a consent encounter, targeted to be within 72 hours of enrolment. However, we will

encourage an *a priori* informed consent whenever possible. The SDM response will be used to continue all trial procedures or any further data collection. If the patient or substitute decision maker declines enrolment, then the patient will be excluded, and all data obtained using deferred consent will be confidentially destroyed. In addition, once the patient has regained capacity according to the medical team, the patient will be approached to affirm or withdraw consent. Each site will be provided with patient identification numbers, which will be assigned sequentially when a patient is enrolled and will be used in all study documentation to ensure patient confidentially and anonymity. All eligible patients will be recorded on a screening log, which will include their study ID, date of consent, or reason the patient could not be enrolled. The de-identified screening log will be forwarded to the lead project coordinator on a monthly basis. The individual site research coordinators and investigators will be responsible for ensuring the ethical conduct of this trial, screening patients, obtaining consent, and training of staff as needed. The principal investigators and co-investigators will review monthly compliance with the study protocol and recruitment rates.

Confidentiality: To ensure patient confidentiality, identifying information will not be collected on the Case Report Form. Patients will be identified to the coordinating centre only by their unique study identification number. The site study coordinator will maintain a participant master list including the participant name and linked study ID. At the end of the study, this master list will be destroyed. In accordance with current requirements, we will store the de-identified data for a minimum of 10 years.

Data Collection:

rSO_2, hemodynamics, medications, and clinical characteristics: Patients will be enrolled within the first 24 hours of their ICU admission. Immediately following enrolment, the patient will

undergo rSO_2 monitoring. A sensor will be placed in the centre of the patient's forehead, which is attached to the FORESIGHT ELITE oximeter (CASMED, Caster Medical, Canada). This device will provide continuous quantification of rSO_2, every 2 seconds, for 72 hours. To assess the association between hemodynamics and rSO_2 recordings, we will use a commercially available system (Bedmaster, Excel Medical Electronics, FL, USA; or site equivalent) to capture the following vital signs from enrolled patients: heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and peripheral oxygen saturation (SpO_2). These data are captured locally and uploaded to the eCRF (REDCap). Throughout this 72-hour period of recording, we will document adminstered continuous infusion and intermittent bolus doses of vasoactive and sedative/analgesic medications, which will be converted to either "fentanyl equivalents" for narcotics, or "midazolam equivalents" for benzodiazepine medications. These conversion formulas have been previously described.[19] Severity of illness will be measured during the first 24 hours of ICU admission using the Acute Physiology and Chronic Health Evaluation II score (APACHE II). Pre-existing frailty will be assessed upon enrolment using the clinical frailty scale,[20] which is 9-point scale (e.g., 1 = very fit to 9 = terminally ill). All clinical data will be captured on the eCRF.

Central venous and arterial blood collection: Both arterial and central venous gases will be sampled every 12 hours during the 72h period of rSO_2 recording and will include: pH, partial pressure of oxygen (pO_2), partial pressure of carbon dioxide (pCO_2), and hemoglobin concentration (Hb). These blood samples will be collected only if a central line (PICC, internal jugular, subclavian) and arterial line are *already* in place.

Delirium screening: Patients will be assessed daily for delirium throughout their entire hospital stay (ICU and ward; up to day 30) using validated screening tools; the Confusion Assessment

Method (CAM)-ICU[21], as well as the brief Confusion Assessment Method (bCAM)[22] which will be administered on the ward. From the CAM-ICU, the CAM-ICU 7 (i.e., 7-point delirium severity scale) will also be documented (i.e., 0-2: no delirium, 3-5: mild to moderate delirium, and 6-7: severe delirium).[23] The ICU discharge day will be considered to be the day that the attending writes orders to discharge, in order to avoid the influence of delayed discharge.

Determination of pre-existing cognitive impairment: Our pilot study[16] excluded 10% of patients with a documented history of cognitive impairment in their medical chart, which may limit external validity. Importantly, individuals may have substantial cognitive impairment prior to enrolment but did not receive any formal diagnosis. To address this potential confound, all patients will be assessed, upon enrolment, using the clinical dementia rating (CDR) scale.[24] The CDR is a scale from 0 (Normal) to 3 (severe dementia) that is calculated from a standardized scoring sheet completed by interviewing a patient or their caregiver. All staff completing the interview and scoring sheet will undergo rigorous online training and pass a certification exam. A diagnosis of pre-existing cognitive impairment will be defined as a CDR >1.

3- and 12-Month Follow Up:

Neuropsychological assessment: Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): Participants will complete a 3- and 12-month follow up assessment in which the RBANS will be administered by a trained researcher. The RBANS assesses global cognition, as well as several subdomains (i.e., immediate and delayed memory, visuospatial/constructional, language, and attention). These indices have been described previously,[25] and survivors will be compared to age-matched controls. To improve follow up rates, in home/hospital testing will be

performed for individuals not able to return for laboratory assessment. Participant scores are converted to standardized values in which the normative range will be considered a mean of 100+/-24.75 (1.65 SD). Participants that score >75 will not be considered impaired, as these subjects are performing within or above the normative range. The RBANS assessment requires ~20-30 minutes to complete.

KINARM Assessment: Participants (from the Kingston region only) will complete a 3- and 12-month follow up assessment using the End-Point bimanual KINARM robot (BKIN Technologies, Kingston). With each hand, the seated subject grasps a handle attached to a planar robotic device that permits movements in the horizontal plane with an integrated virtual reality system that presents objects in the horizontal plane (Figure 2). Subjects will perform a behavioural battery to quantify a broad range of sensorimotor, and cognitive function using their upper limbs. A trained operator selects a task from the software menu, reads the standardized instructions, and then monitors performance in real-time. We will administer 7 tasks from the KINARM Standard Tests™ including: Spatial Span (SS, Figure 3A), Visually Guided Reaching (VGR, Figure 3B), Reverse Visually Guided Reaching (RVGR, Figure 3B), Ball on Bar (BonB, Figure 3C), Arm Position Matching (APM, Figure 3D), Object Hit (OH, see Figure 3E), Object Hit and Avoid (OHA, see Figure 3F). Each task has been previously described,[26] and quantifies subject performance using approximately 6 to 12 metrics per task. Each metric is converted into normalized units based on healthy subject performance, considering the influence of sex, age, and handedness (0 is mean performance and ±1 is a standard deviation from the mean). For each task, a task score will also be generated to provide a global performance measure with values that are equivalent to standard deviation units with zero specifying best possible performance, and higher values indicating worse performance. Therefore, performance will be considered

abnormal if the task score is outside the +1.96 range (i.e., 5th percentile). The task score has been previously described.[27] The KINARM assessment takes ~45 minutes to complete.

Sample Size Calculation:

Primary Outcome: Our overall hypothesis is that poor cerebral perfusion contributes to delirium and long-term cognitive impairment. For study purposes, we define poor cerebral perfusion as the composite of 1) low mean rSO_2, 2) duration of impaired cerebral autoregulation, and 3) time outside individualized optimal MAP (MAP_{OPT}), which will be discussed in more detail in the statistical plan section. We acknowledge that this in an imperfect measure of cerebral perfusion. However, this is a comprehensive, continuous, and non-invasive assessment of cerebral perfusion. For our primary outcome (CAM-7 delirium severity score), we plan to assess approximately 400 patients, to allow 10 degrees of freedom for our 3 measures of perfusion (i.e., mean rSO_2, duration of disturbed cerebral autoregulation, duration outside MAP_{OPT}) and controlling for the 9 covariates (see below). The 10 degrees of freedom will allow us to model non-linear relationships between the 3 measures of cerebral perfusion and delirium severity. This sample size achieves 90% power to detect an R^2 of 0.050 collectively among these measures of cerebral perfusion and using an F-test with a significance level (alpha) of 0.050 (see Figure 4). In order to have ≥400 patients to assess, we will enrol 500 patients, as our prior work has demonstrated that ~20% of patients remain comatose (RASS = -4 or -5) during their entire ICU stay[16], and cannot be assessed for delirium.

Secondary Outcomes-Physiological determinants of rSO_2 and neurological outcomes

For evaluating the determinants of the rSO_2 signal, we will assess the association between each of the 9 pre-specified candidate predictors of rSO_2 after controlling for the 4 co-variates (see

below for co-variates). 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 described[18] 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.

However, we will define cerebral autoregulation dysfunction by using a statistical significance threshold for positive COx correlation values ($p<0.0001$). Cumulative duration of disturbed autoregulation will be given by the duration of time spent with a significant positive correlation throughout the period of neuromonitoring. Computer algorithms for COx will be developed and implemented blind to the neurological status of enrolled patients.

Estimating optimal MAP: To calculate the individualized optimal MAP (MAP_{OPT}), the computed COx values will be binned by the average MAP value in their respective moving windows in 5 mmHg bins.[29] An alternative strategy will also be implemented. We will invert the MAP_{OPT} binning procedure by binning MAP values by their corresponding COx values in sequential 0.05 bins of Spearman correlation coefficients ranging from -1 to +1. This procedure has been previously described.[18]

Assessment of primary outcome: Multivariate linear regression will be used to characterize the association between adequate cerebral perfusion (as measured using duration of time (minutes) outside of MAP_{OPT}, mean rSO_2, and duration of disturbed cerebral autoregulation) and delirium severity throughout a patient's ICU stay to determine if poor cerebral oxygenation is an independent predictor of delirium. We will estimate the unadjusted effect of each individual predictor on delirium severity (i.e., cumulative CAM-7 scores per patient). The simultaneous multivariate regression model will adjust for the following covariates due to their potential associations with delirium: a history of hypertension, a history of alcohol abuse, total sedative dose (in midazolam equivalents), total narcotic dose (in fentanyl equivalents), severity of illness (APACHE II scores), pre-existing cognitive impairment (CDR score), length of ICU stay, frailty, (clinical frailty scale) and blood urea nitrogen. The multivariable model will provide the adjusted regression coefficients after controlling for all predictors included in the model. All covariates

included in regression modeling have been chosen *a priori* based on clinical judgment and previous research.[16,30] Model diagnostics will be conducted to assess the underlying assumptions of linear regression (i.e., linearity, normally distributed residuals, equal variances, and lack of multicolinearity) for all models. Multiple imputation strategies will be applied at the time of the regression modeling to account for any missing data and reduce bias associated with excluding patients due to partially collected data.

Secondary outcomes:

Determinants of rSO_2: To assess the hemodynamic and physiological determinants of rSO_2 at the patient level, multiple linear regression will be performed using the patient average of each variable over the 72-hour data collection period. The following predictors will be included in the regression model: HR, SpO_2, MAP, arterial, and venous blood gas data (i.e., pH, pO_2, and pCO_2), central venous oxygen saturation, and Hb concentration. In addition, the multivariate model will control for the following covariates associated with cerebral perfusion: age,[31] as well as total sedative, narcotic, and vasopressor dosing. Simultaneous multiple linear regression with adjustment for all aforementioned covariates will be implemented. As stated for the primary outcome regression analysis, model diagnostics will be performed. Furthermore, the relationship between the determinants of the NIRS-derived rSO_2 signal may vary over time (see Figure 6 and Supplemental Movie 1). Therefore, a repeated measures analysis will also be performed by using multilevel modeling with 6 observations reflecting each 12-hour period during the 72-hour data collection period (with time coded as 0 – 5, so the intercept equals baseline/time of enrolment) nested within each subject. The predictors will be the same as the regression model but allowed to be time varying across the 6 observation points. This analysis will assess if within patient

changes in the predictors correlate with changes in rSO_2, and if these associations are modified by fixed patient characteristics, such as age.

Assessing if poor cerebral perfusion during critical illness is a significant predictor of long-term neurological dysfunction among ICU survivors: Multiple linear regression analysis will be used to assess if impaired cerebral perfusion (i.e., time below MAP_{OPT}, mean rSO_2, and duration of disturbed cerebral autoregulation) is associated with RBANS global cognition scores at 3- and 12-months post-ICU discharge. We will use the following clinical covariates collected on admission (i.e., pre-existing cognitive impairment, age, severity of illness, frailty) and data collected within the first 72 hours of the patients' ICU stay (i.e., narcotic dosing and benzodiazepine dosing). All covariates will be adjusted for in separate regression models for the cognitive outcomes at 3- and 12-months post-ICU discharge. If global cognition is significantly predicted by the time below MAP_{OPT}, we will conduct an exploratory analysis of the RBANS subdomains of cognition (i.e., delay and immediate memory, language, attention, visuospatial/constructional) adjusting for the aforementioned covariates to further explore specific areas of impairment observed among survivors of critical illness. Only patients assessed at KHSC will undergo KINARM testing, so this data will be assessed with descriptive statistics only to avoid any potential bias.

DISCUSSION

This multicentre observational study will extend our preliminary findings of reduced rSO_2 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 rSO_2 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 rSO_2. It will lay the foundation for a larger interventional study designed to assess whether optimization of rSO_2 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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Acknowledgments:

The authors would like to thank the study coordinators, Ms. Miranda Hunt, Ms. Ilinca Georgescu, and Mrs. Tracy Boyd, as well as the entire KHSC ICU staff for their continued support of our clinical research. This manuscript underwent an internal peer-review process with the Canadian Critical Care Trials Group, and we are greatly appreciative of the helpful contributions made by both Dr. Lisa Burry and Dr. Pierre Cardinal. We would also like to thank the KINARM technologists, Ms. Simone Appaqaq, Ms. Kim Moore, and Ms. Helen Bretzke.

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

pCO_2: Arterial Partial Pressure of Carbon Dioxide

PICS: Post-intensive Care Syndrome

pO_2: Arterial Partial Pressure of Oxygen

RASS: Richmond Agitation and Sedation Scale

RBANS: Repeatable Battery for the Assessment of Neuropsychological Status

rSO_2: Regional Cerebral Oxygenation

RVGR: Reverse Visually Guided Reaching

SpO_2: Peripheral Oxygen Saturation

SS: Spatial Span

SDM: Substitute Decision Maker

VGR: Visually Guided Reaching

Authors' contributions:

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

JK participated in study design and drafting of the manuscript.

KL participated in study design and drafting of the manuscript.

DM participated in study design and drafting of the manuscript.

JM participated in study design and drafting of the manuscript.

MH participated in study design and drafting of the manuscript.

SHS participated in study design and drafting of the manuscript.

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

JAJ participated in statistical planning and drafting of the manuscript.

IB participated in study design and drafting of the manuscript.

MS participated in study design and drafting of the manuscript.

NO participated in study design and drafting of the manuscript.

SE participated in study design and drafting of the manuscript.

VM participated in study design and drafting of the manuscript.

MC participated in study design and drafting of the manuscript.

DG participated in study design and drafting of the manuscript.

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

Funding statement:

This work was supported by the Physician Services Incorporated and the Southeastern Ontario Academic Medical Organization New Clinician Scientist Program for which JGB was the

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

Competing interests statement.

Mr. Michael D. Wood has nothing to disclose.

Ms. Jasmine Khan has nothing to disclose.

Dr. Kevin Lee has nothing to disclose.

Dr. David Maslove has nothing to disclose.

Dr. John Muscedere is the scientific director of the Canadian Frailty Network.

Ms. Miranda Hunt has nothing to disclose.

Dr. Stephen Scott is the cofounder of BKIN Technologies, the manufacturer of the KINARM device.

Mr. Andrew Day has nothing to disclose.

Dr. Jill Jacobson has nothing to disclose.

Dr. Ian Ball receives a stipend from the Trillium Gift of Life Network to support his role as a Regional Medical Lead.

Dr. Niamh O'Regan received funding from the Academic Medical Organization of Southwestern Ontario.

Dr. Marat Slessarev receives a stipend from the Trillium Gift of Life Network to support his role as a Hospital Donation Physician.

Dr. Victoria McCredie has nothing to disclose.

Dr. Shane English has nothing to disclose.

Dr. Donald Griesdale is funded through a Health-Professional Investigator Award from the Michael Smith Foundation for Health Research.

Dr. J. Gordon Boyd receives a stipend from the Trillium Gift of Life Network to support his role as a Regional Medical Lead.

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 abilities[32] 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.

Figure 4. A power curve indicating the study sample size, and the respective statistical power, to asses the primary study outcome. *Note.* Red dots represent the sample size needed for a given statistical power. The primary sample size was calculated using the following multivariate regression model parameters: 10 independent variables tested, controlling for 9 additional covariates, power = 0.90, $R^2 = 0.050$, $\alpha = 0.05$, which would require a sample size of 400.

Figure 5A. Simplified line graph (24 hours instead of the full 72 hour recording period) illustrating the sliding window correlation between mean arterial pressure and regional brain tissue oxygenation for an individual patient over a 24 period of recording. *Note*. The black rectangle represents a 60-minute window that moves forward 1-minute at a time until the recording period is completed. **B**. Scatter plot illustrating a time dependent positive association between mean arterial pressure and regional brain tissue oxygenation. *Note*. Black dots represent data collected for an individual patient over 24 hours, with the blue line representing a linear model fit to the data, and the grey shaded region representing the 95% confidence interval. **C**. Scatter plot indicating the time varying association between mean arterial pressure and regional brain tissue oxygenation represented as the cerebral oximetry index (COx) over an individual patient's 24-hour recording period. *Note*. A positive Cox values (>.3) represents dysfunctional cerebral autoregulation, with negative or near zero values indicating intact cerebral autoregulation.

Figure 6. Line graph of the high frequency vital sign recordings indicates the highly variable relationships with regional brain tissue oxygenation over the 72-hour period of recording. *Note*. The figure represents a single patient's ICU recording. rSO_2 = Regional brain tissue oxygenation; HR = Heart rate; SpO_2 = Arterial oxygen saturation; artMAP= Mean arterial pressure from an arterial line.

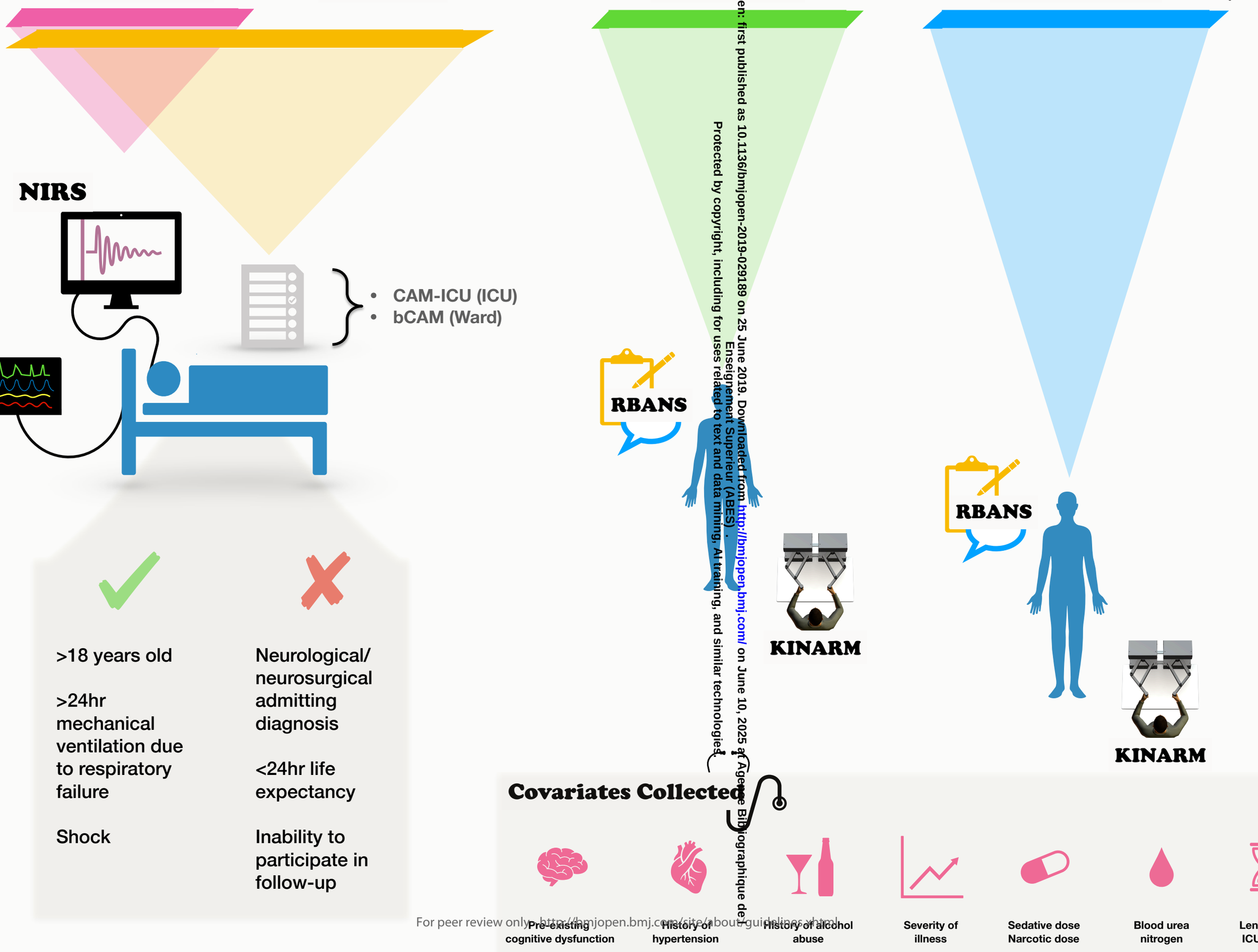
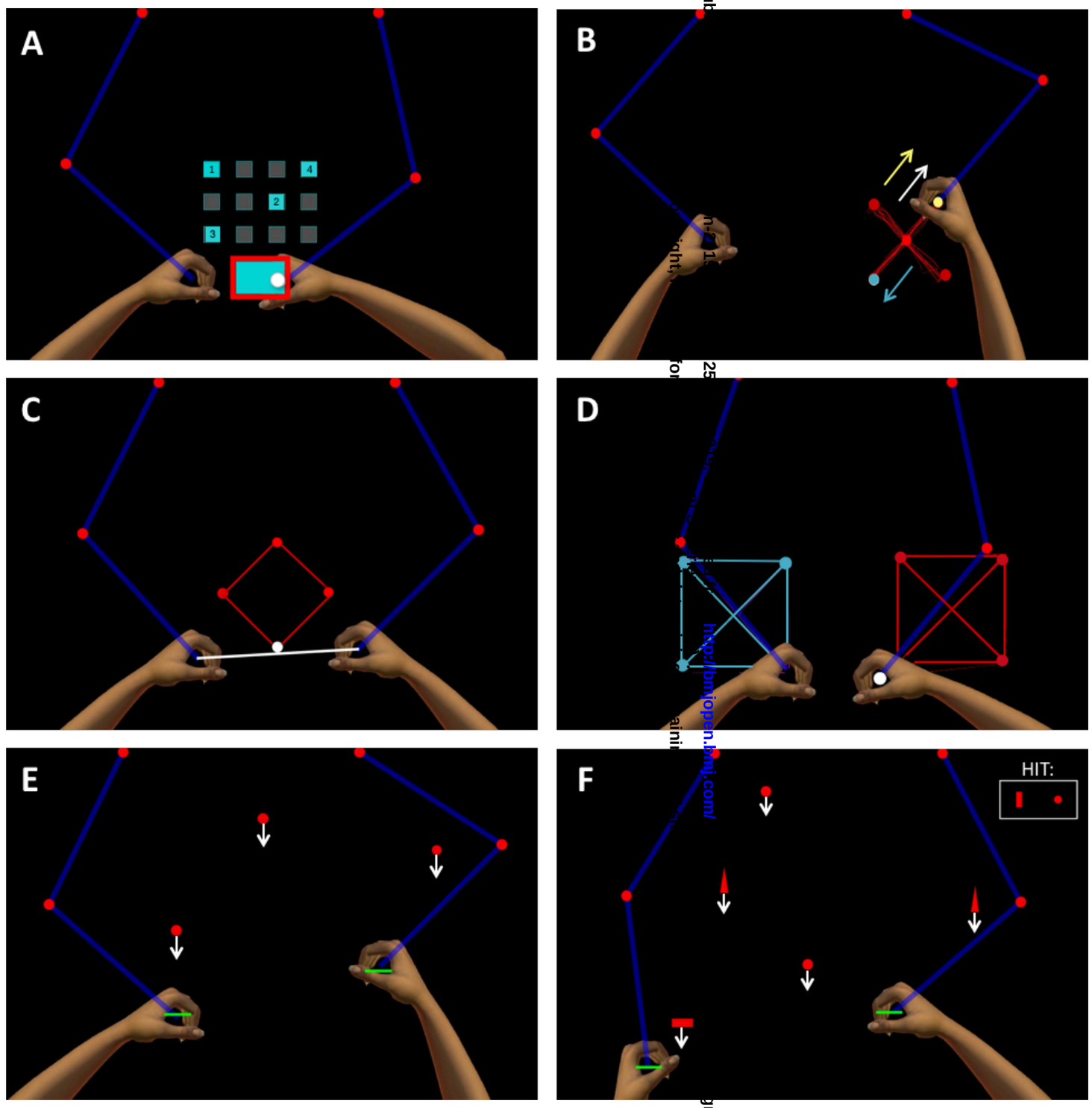
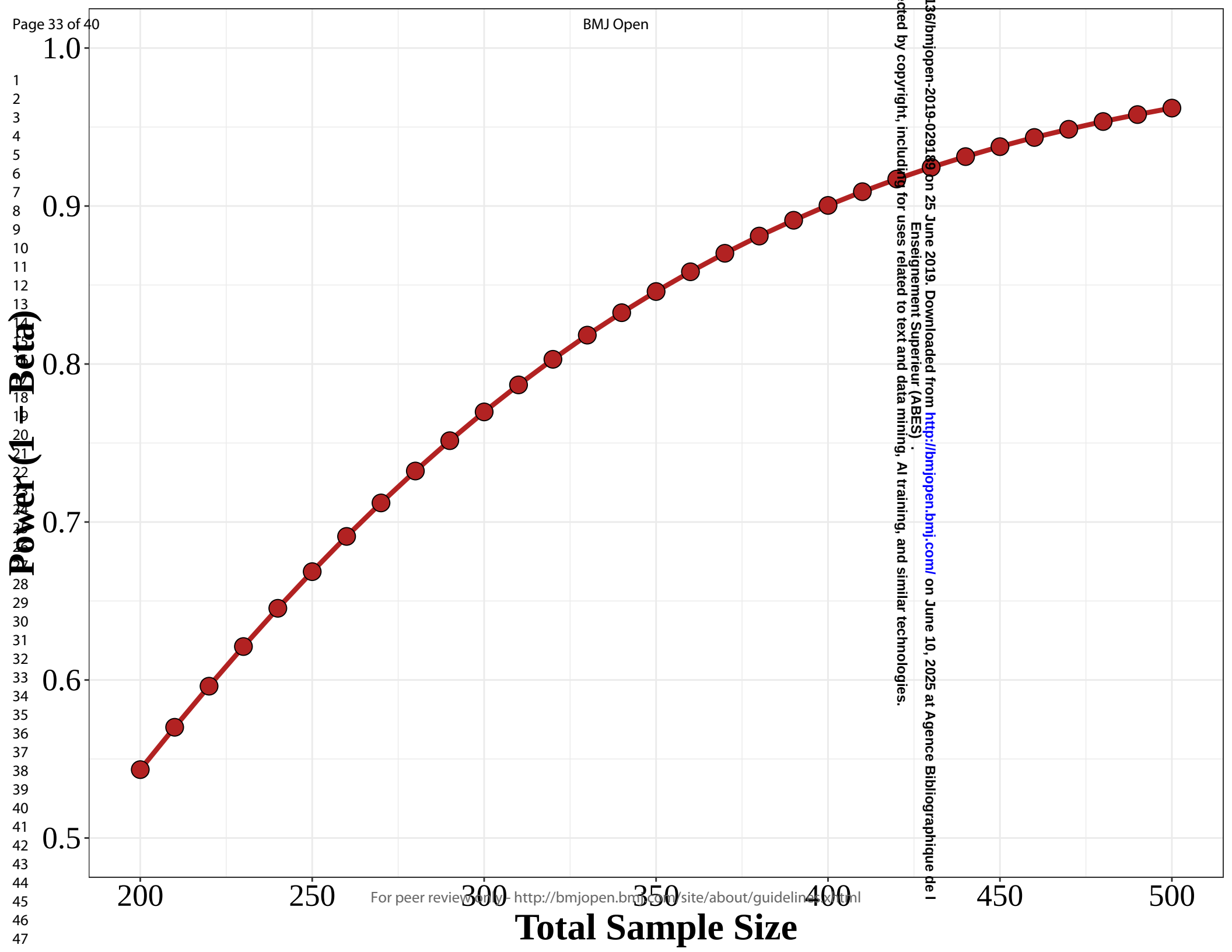
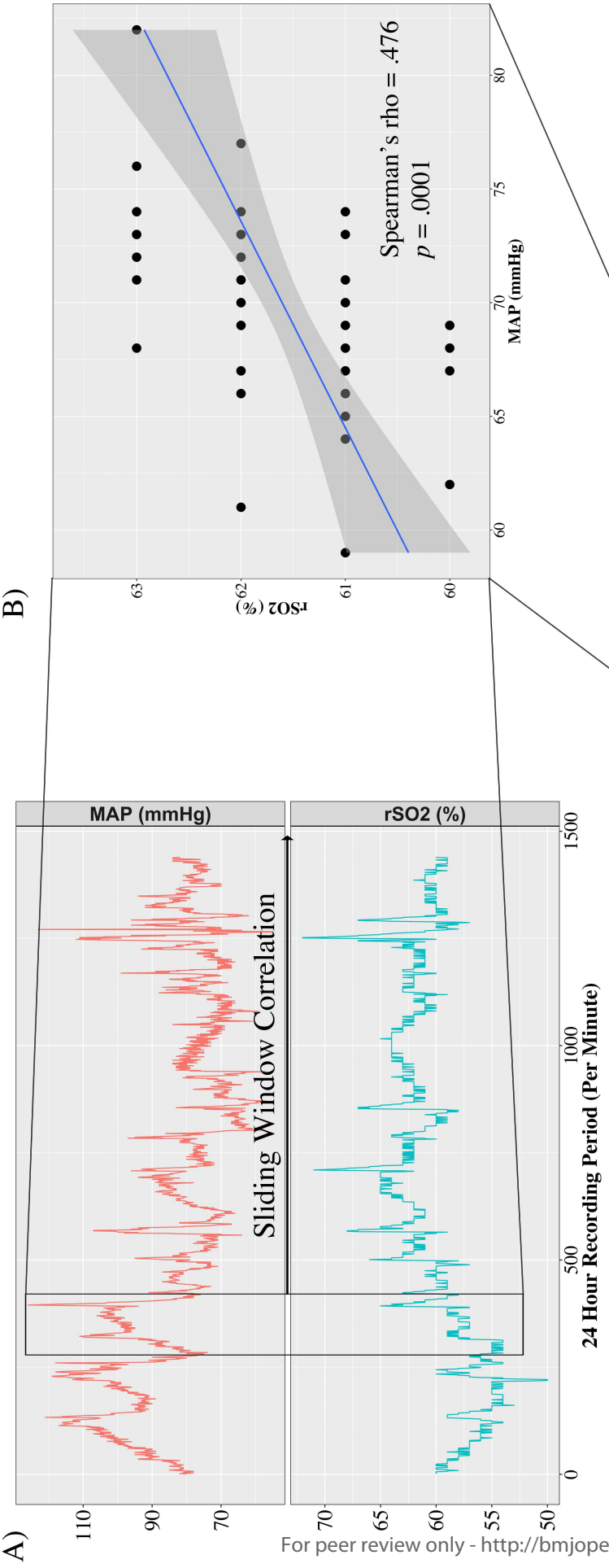


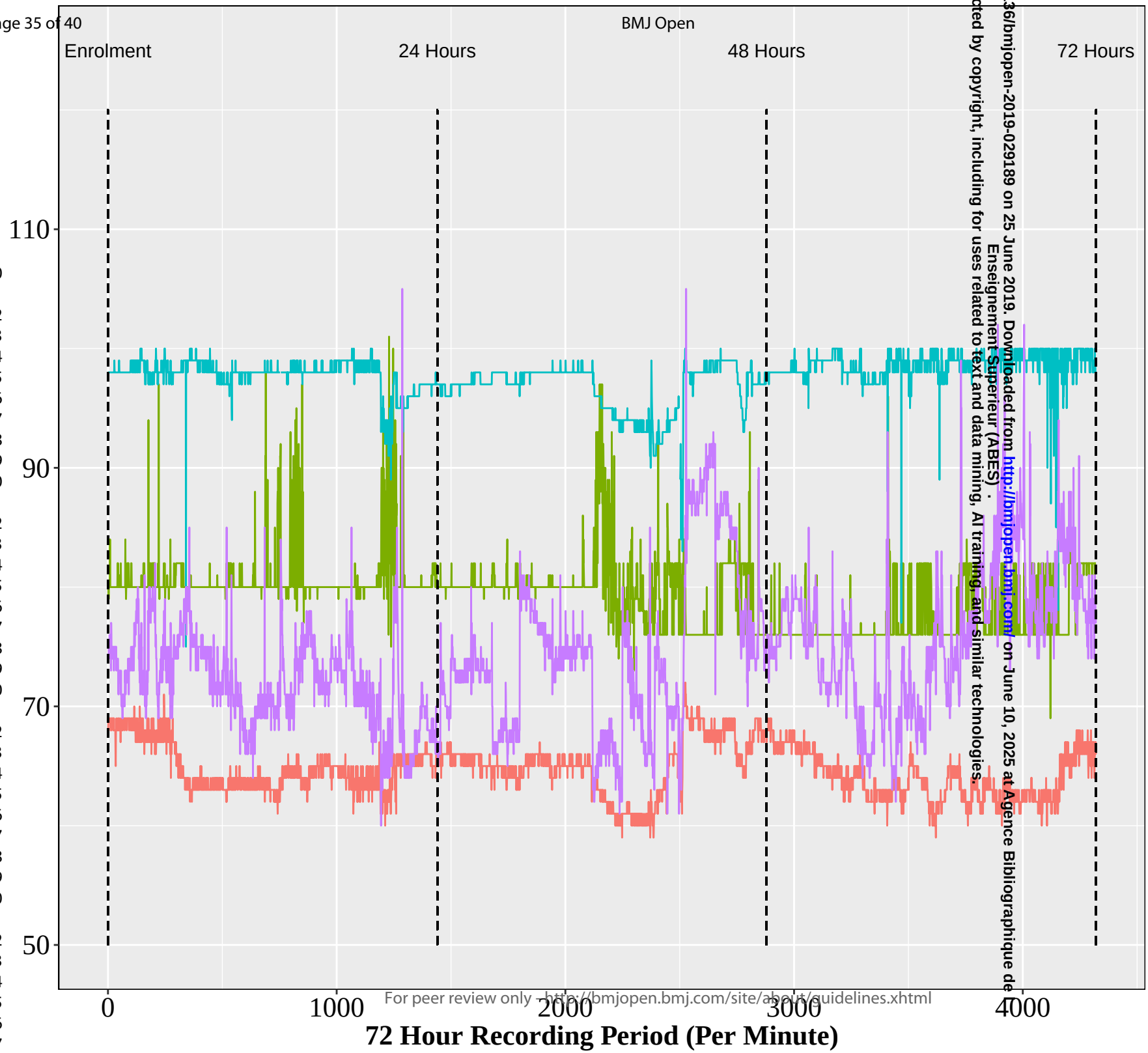
Figure 2. Three-dimensional animated representation of the KINARM End-Point robotic set-up used at 3- and 12-month follow up assessments.

320x299mm (72 x 72 DPI)









SPIRIT

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			

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
	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
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
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
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15-18
	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
Methods: Monitoring			
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
	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:	*BMJ Open*
Manuscript ID	bmjopen-2019-029189.R1
Article Type:	Protocol
Date Submitted by the Author:	03-Apr-2019
Complete List of Authors:	Wood, Michael; Queen's University, Centre For Neuroscience Studies Khan, Jasmine; Queen's University, Centre for Neuroscience Studies Lee, Kevin; Queen's Univeristy, School of Medicine Maslove, David M; Queen's University , Critical Care Medicine Muscedere, John; Kingston General Hospital, Critical Care Medicine Hunt, Miranda; Queen's University, Critical Care Medicine Scott, Stephen; Queen's University, Centre for Neuroscience Studies Day, Andrew ; Queen's Unversity, Department of Community health and Epidemiology and CERU Jacobson, Jill; Queen's University, Psychology Ball, Ian; London Health Sciences Centre, Medicine Slessarev, Marat; Western University, Medicine, Division of Geriatric Medicine O'Regan, Niamh; Western University, Medicine, Division of Geriatric Medicine English, Shane; University of Ottawa, Medicine (Critical Care); Ottawa Hospital Research Institute, Clinical Epidemiology Program McCredie, Victoria; University of Toronto; Toronto Western Hospital, University Health Network, Medicine; Critical Care Chasse, Michaël; Centre Hospitalier de L'Universite de Montreal, Medicine (Critical Care) Griesdale, Donald; University of British Columbia, Department of Anesthesiology, Pharmacology & Therapeutics Boyd, John; Kingston General Hospital, Critical Care Medicine
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.

Supplemental Figure 1.gif

Title: 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

Authors: The Cerebral Oxygenation and Neurological Outcomes Following Critical Illness (CONFOCAL) Research Group

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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 (rSO_2) to assess the association between poor rSO_2 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 rSO_2 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, rSO_2 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

peer review. Results will also be presented at national/international scientific conferences. Upon completion, the study findings will be submitted for publication in peer-reviewed journals.

Trial Registration: This trial is registered on clinicaltrials.gov (Identifier: NCT03141619), registered May 5, 2017.

Key Words: Near-infrared spectroscopy; Cerebral oximetry; Cerebral autoregulation; KINARM, Delirium; CAM-ICU; Post-intensive care syndrome; RBANS

Strengths and Limitations of this study:

- Potential to replicate our previous work in a representative cohort and further assess the association between poor regional cerebral oxygenation (rSO_2) and ICU associated.
- Further assessment of dysfunctional cerebral autoregulation as a potential underlying mechanism associated with the development of delirium and post-intensive care unit (ICU) impairment.
- Using multiple regression to further characterize the physiological determinants of the near-infrared spectroscopy (NIRS) derived signal has the potential to lead to the development of a novel resuscitation target during critical care.
- Although this study is observational in nature, which limits causal inferences, correlating neurophysiological and cognitive performance metrics may identify modifiable risk factors (e.g., disturbed autoregulation duration) during critical care.
- Understanding the determinants of the NIRS signal may revolutionize critical care by providing clinicians with the ability to implement precision-based medicine, and optimize cerebral oxygenation to preserve neurological function.

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 known as the KINARM, which uses the participant's upper limbs to asses sensorimotor and cognitive function,has indicated that ICU survivors also develop visuospatial and motor deficits.[9] Importantly, when assessed using the Repeatable Battery for Neuropsychological Status (RBANS), many critical illness survivors had performance scores 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.

This issue has resulted in a limited number of studies investigating the influence of cerebral perfusion on delirium in critically ill patients (Reviewed in[11]). Near-infrared spectroscopy (NIRS) is a non-invasive technology that measures regional cerebral oxygenation (rSO_2) as a surrogate marker of cerebral perfusion,[12,13] as rSO_2 values correlate with other markers of cerebral perfusion, including CT perfusion, jugular venous bulb oxygen saturation, and brain tissue oxygen tension.[12–14] Therefore, NIRS is an ideal candidate for both ICU research and clinical practice.

Feasibility and single-center prospective ICU studies have been performed with NIRS, discovering that low rSO_2 is an independent risk factor for the development of delirium.[15,16] A nested cohort in this study demonstrated that impaired cerebral auto-regulation (i.e., the ability to maintain stabilized and adequate cerebral perfusion) is also associated with the development and duration of delirium.[17,18] While these findings were statistically significant, a multi-centre observational study is necessary for external validation and the study of long-term outcomes.

Our overarching hypothesis is that decreased rSO_2 in the early stages of critical illness leads to the development of delirium, as well as long-term cognitive impairment among survivors. The primary objective is to further establish an association between poor cerebral perfusion and delirium severity. Secondary objectives include assessing the hemodynamic and physiological determinants of rSO_2, as well as to identify potential risk factors (e.g., poor rSO_2) associated with delirium and long-term cognitive deficits. Overall, elucidating the mechanisms of acute and chronic neurological impairment will allow for the development of preventative 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 study[16] 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,

neuromuscular disorders). Post-cardiac arrest patients are also excluded from this study. Additional study sites will include the following: Toronto Western Hospital (Site PI Dr. Victoria McCredie), Université de Montreal (Montreal, QC; Site PI Dr. Michael Chasse), London Health Sciences Centre-Victoria Hospital (London, ON; Site PI Dr. Ian Ball, with co-PIs Dr. Marat Slesserev and Dr. Niamh O'Reagan), Ottawa General Hospital (Site PI Dr. Shane English), Ottawa Civic Hospital (Site PI Dr. Shane English), and Vancouver General Hospital (Site PI Dr. Donald Griesdale). KHSC is responsible for developing and maintaining the electronic case report forms (eCRF), data management, and analysis.

Recruitment and consent: The Queen's University and Affiliated Hospitals Health Sciences Research Ethics Board will serve as the board of record for the streamlined research ethics review system (Clinical Trials Ontario) and all Ontario sites have gained approval; Non-Ontario sites will need to obtain local ethics approval at their earliest convenience. All patients admitted to the ICU will be screened daily for eligibility. The participant will be approached by a member of the research staff. If the participant is unable to provide consent, the research staff will approach the Substitute Decision Maker (SDM). The research coordinator or trained study staff will obtain informed consent and documentation of the consent process will be noted in the patient's medical chart. As patients meeting eligibility criteria are unlikely to be able to give informed consent at the time of enrolment due to their critical condition, we will employ a deferred consent model when appropriate (e.g., SDMs are frequently in an emotional state and may not be available to be contacted), which has already been granted local research ethics board approval. When an SDM is not available to approach, we will enrol the patient and begin trial procedures until the SDM is available for a consent encounter, targeted to be within 72 hours of

enrolment. However, we will encourage an *a priori* informed consent whenever possible. The SDM response will be used to continue all trial procedures or any further data collection. If the patient or substitute decision maker declines enrolment, then the patient will be excluded, and all data obtained using deferred consent will be confidentially destroyed. In addition, once the patient has regained capacity according to the medical team, the patient will be approached to affirm or withdraw consent. Each site will be provided with patient identification numbers, which will be assigned sequentially when a patient is enrolled and will be used in all study documentation to ensure patient confidentially and anonymity. All eligible patients will be recorded on a screening log, which will include their study ID, date of consent, or reason the patient could not be enrolled. The de-identified screening log will be forwarded to the lead project coordinator on a monthly basis. The individual site research coordinators and investigators will be responsible for ensuring the ethical conduct of this trial, screening patients, obtaining consent, and training of staff as needed. The principal investigators and co-investigators will review monthly compliance with the study protocol and recruitment rates.

Confidentiality: To ensure patient confidentiality, identifying information will not be collected on the Case Report Form. Patients will be identified to the coordinating centre only by their unique study identification number. The site study coordinator will maintain a participant master list including the participant name and linked study ID. At the end of the study, this master list will be destroyed. In accordance with current requirements, we will store the de-identified data for a minimum of 10 years.

Data Collection:

rSO_2, hemodynamics, medications, and clinical characteristics: Patients will be enrolled within the first 24 hours of their ICU admission. Immediately following enrolment, the patient will

undergo rSO_2 monitoring. A sensor will be placed in the centre of the patient's forehead, which is attached to the FORESIGHT ELITE oximeter (CASMED, Caster Medical, Canada). This device will provide continuous quantification of rSO_2, every 2 seconds, for 72 hours. To assess the association between hemodynamics and rSO_2 recordings, we will use a commercially available system (Bedmaster, Excel Medical Electronics, FL, USA; or site equivalent) to capture the following vital signs from enrolled patients: heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and peripheral oxygen saturation (SpO_2). These data are captured locally and uploaded to the eCRF (REDCap). Throughout this 72-hour period of recording, we will document adminstered continuous infusion and intermittent bolus doses of vasoactive and sedative/analgesic medications, which will be converted to either "fentanyl equivalents" for narcotics, or "midazolam equivalents" for benzodiazepine medications. These conversion formulas have been previously described.[19] Severity of illness will be measured during the first 24 hours of ICU admission using the Acute Physiology and Chronic Health Evaluation II score (APACHE II). Trained research staff will approach whomever provided informed consent (i.e., either the patient or the SDM) to ascertain the enrolled patient's pre-existing frailty (i.e., prior to ICU admission) using the clinical frailty scale,[20] which is 9-point scale (e.g., 1 = very fit to 9 = terminally ill). All clinical data will be captured on the eCRF.

Central venous and arterial blood collection: Both arterial and central venous gases will be sampled every 12 hours during the 72h period of rSO_2 recording and will include: pH, partial pressure of oxygen (pO_2), partial pressure of carbon dioxide (pCO_2), and hemoglobin concentration (Hb). These blood samples will be collected only if a central line (PICC, internal jugular, subclavian) and arterial line are *already* in place.

Delirium screening: Patients will be assessed once daily for deliriumthroughout their entire hospital stay (ICU and ward; up to day 30) using validated screening tools; the Confusion Assessment Method (CAM)-ICU[21], as well as the brief Confusion Assessment Method (bCAM)[22] which will be administered on the ward. Both delirium screening tools will be administered by trained research staff at a time that is convenient for the patient, their family, and the medical team directing their care.

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

Determination of pre-existing cognitive impairment: Our pilot study[16] excluded 10% of patients with a documented history of cognitive impairment in their medical chart, which may limit external validity. Importantly, individuals may have substantial cognitive impairment prior to enrolment but did not receive any formal diagnosis. To address this potential confound, all patients will be assessed, upon enrolment, using the clinical dementia rating (CDR) scale.[24] The CDR is a scale from 0 (Normal) to 3 (severe dementia) that is calculated from a standardized scoring sheet completed by interviewing a patient or their caregiver. All staff completing the interview and scoring sheet will undergo rigorous online training and pass a certification exam. A diagnosis of pre-existing cognitive impairment will be defined as a CDR >1.

3- and 12-Month Follow Up:

Neuropsychological assessment: Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): Participants will complete a 3- and 12-month follow up assessment in which the RBANS will be administered by a trained researcher. The RBANS assesses global cognition, as well as several subdomains (i.e., immediate and delayed memory, visuospatial/constructional, language, and attention). These indices have been described previously,[25] and survivors will be compared to age-matched controls. To improve follow up rates, in home/hospital testing will be performed for individuals not able to return for laboratory assessment. Participant scores are converted to standardized values in which the normative range will be considered a mean of 100+/-24.75 (1.65 SD). Participants that score >75 will not be considered impaired, as these subjects are performing within or above the normative range. The RBANS assessment requires ~20-30 minutes to complete.

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

approximately 6 to 12 metrics per task. Each metric is converted into normalized units based on healthy subject performance, considering the influence of sex, age, and handedness (0 is mean performance and ±1 is a standard deviation from the mean). For each task, a task score will also be generated to provide a global performance measure with values that are equivalent to standard deviation units with zero specifying best possible performance, and higher values indicating worse performance. Therefore, performance will be considered abnormal if the task score is outside the +1.96 range (i.e., 5th percentile). The task score has been previously described.[33] The KINARM assessment takes ~45 minutes to complete.

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 described[18] and a visual representation can be observed in Figure 3. 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. However, we will define cerebral autoregulation dysfunction by using a statistical significance threshold for positive COx correlation values ($p<0.0001$). Cumulative duration of disturbed autoregulation will be given by the duration of time spent with a significant positive correlation

throughout the period of neuromonitoring. Computer algorithms for COx will be developed and implemented blind to the neurological status of enrolled patients.

Estimating optimal MAP: To calculate the individualized optimal MAP (MAP_{OPT}), the computed COx values will be binned by the average MAP value in their respective moving windows in 5 mmHg bins.[34] An alternative strategy will also be implemented. We will invert the MAP_{OPT} binning procedure by binning MAP values by their corresponding COx values in sequential 0.05 bins of Spearman correlation coefficients ranging from -1 to +1. This procedure has been previously described.[18]

Assessment of primary outcome: Multivariate linear regression will be used to characterize the association between adequate cerebral perfusion (as measured using duration of time (minutes) outside of MAP_{OPT}, mean rSO_2, and duration of disturbed cerebral autoregulation) and delirium severity throughout a patient's ICU stay to determine if poor cerebral oxygenation is an independent predictor of delirium. We will estimate the unadjusted effect of each individual predictor on delirium severity (i.e., cumulative CAM-7 scores per patient). The simultaneous multivariate regression model will adjust for the following covariates due to their potential associations with delirium: a history of hypertension, a history of alcohol abuse, total sedative dose (in midazolam equivalents), total narcotic dose (in fentanyl equivalents), severity of illness (APACHE II scores), pre-existing cognitive impairment (CDR score), length of ICU stay, frailty, (clinical frailty scale) and blood urea nitrogen. The multivariable model will provide the adjusted regression coefficients after controlling for all predictors included in the model. All covariates included in regression modeling have been chosen *a priori* based on clinical judgment and previous research.[16,35] Model diagnostics will be conducted to assess the underlying assumptions of linear regression (i.e., linearity, normally distributed residuals, equal variances, and lack of

multicolinearity) for all models. Multiple imputation strategies will be applied at the time of the regression modeling to account for any missing data and reduce bias associated with excluding patients due to partially collected data.

Secondary outcomes:

Determinants of rSO_2: To assess the hemodynamic and physiological determinants of rSO_2 at the patient level, multiple linear regression will be performed using the patient average of each variable over the 72-hour data collection period. The following predictors will be included in the regression model: HR, SpO_2, MAP, arterial, and venous blood gas data (i.e., pH, pO_2, and pCO_2), central venous oxygen saturation, and Hb concentration. In addition, the multivariate model will control for the following covariates associated with cerebral perfusion: age,[36] as well as total sedative, narcotic, and vasopressor dosing. Simultaneous multiple linear regression with adjustment for all aforementioned covariates will be implemented. As stated for the primary outcome regression analysis, model diagnostics will be performed. Furthermore, the relationship between the determinants of the NIRS-derived rSO_2 signal may vary over time (see Figure 4 and Supplemental Movie 1). Therefore, a repeated measures analysis will also be performed by using multilevel modeling with 6 observations reflecting each 12-hour period during the 72-hour data collection period (with time coded as 0 – 5, so the intercept equals baseline/time of enrolment) nested within each subject. The predictors will be the same as the regression model but allowed to be time varying across the 6 observation points. This analysis will assess if within patient changes in the predictors correlate with changes in rSO_2, and if these associations are modified by fixed patient characteristics, such as age.

Assessing if poor cerebral perfusion during critical illness is a significant predictor of long-term neurological dysfunction among ICU survivors: Multiple linear regression analysis will be used

to assess if impaired cerebral perfusion (i.e., time below MAP_{OPT}, mean rSO_2, and duration of disturbed cerebral autoregulation) is associated with RBANS global cognition scores at 3- and 12-months post-ICU discharge. We will use the following clinical covariates collected on admission (i.e., pre-existing cognitive impairment, age, severity of illness, frailty) and data collected within the first 72 hours of the patients' ICU stay (i.e., narcotic dosing and benzodiazepine dosing). All covariates will be adjusted for in separate regression models for the cognitive outcomes at 3- and 12-months post-ICU discharge. If global cognition is significantly predicted by the time below MAP_{OPT}, we will conduct an exploratory analysis of the RBANS subdomains of cognition (i.e., delay and immediate memory, language, attention, visuospatial/constructional) adjusting for the aforementioned covariates to further explore specific areas of impairment observed among survivors of critical illness. Due to the limited availability of the KINARM robot across sites, only patients assessed at KHSC will undergo KINARM testing.This data will be assessed with descriptive statistics only to avoid any potential bias introduced by this design.

Sample Size Calculation:

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

= -4 or -5) during their entire ICU stay[16], and cannot be assessed for delirium. Therefore, using our pilot data, we estimate that ~100 patients will be remain comatose resulting in approximately 400 patients to assess our primary outcome, which will allow for 10 degrees of freedom for our 3 measures of perfusion (i.e., mean rSO_2, duration of disturbed cerebral autoregulation, duration outside MAP_{OPT}) and controlling for the 9 covariates (see below). The 10 degrees of freedom will allow us to model non-linear relationships between the 3 measures of cerebral perfusion and delirium severity. This sample size achieves 90% power to detect an R^2 of 0.050 collectively among these measures of cerebral perfusion and using an F-test with a significance level (alpha) of 0.050 (see Figure 5).

Secondary Outcomes-Physiological determinants of rSO_2 and neurological outcomes

For evaluating the determinants of the rSO_2 signal during critical illness, we will assess the association between each of the 9 pre-specified candidate predictors of rSO_2 after controlling for the 4 co-variates (see below for co-variates). We will use a Bonferroni correction (0.05/9=0.0056) to control for multiple testing. With the total 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. However, our pilot data indicated a 30% mortality rate. Given our overall sample size of 500 patients recruited, we are anticipating ~350 ICU survivors (i.e., 500-150) to return for follow up assessment. This cohort will provide sufficient power to detect important predictors of long-term neurological outcomes. However, these predictors have been

intentionally not specified *a priori*, as this analysis will be dependent on our findings related to cerebral perfusion and delirium.

All sample size calculations were conducted using Power Analysis and Sample Size Software (Version 15).[37]

The actual start date at KHSC began on January 26, 2018 and our estimated primary completion data is June 2022. Due to our 12 month follow up, we expect the study to be completed June 2023.

DISCUSSION

This multicentre observational study will extend our preliminary findings of reduced rSO_2 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 rSO_2 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 rSO_2. It will lay the foundation for a larger interventional study designed to assess whether optimization of rSO_2 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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Acknowledgments:

The authors would like to thank the study coordinators, Ms. Miranda Hunt, Ms. Ilinca Georgescu, and Mrs. Tracy Boyd, as well as the entire KHSC ICU staff for their continued support of our clinical research. This manuscript underwent an internal peer-review process with the Canadian Critical Care Trials Group, and we are greatly appreciative of the helpful contributions made by both Dr. Lisa Burry and Dr. Pierre Cardinal. We would also like to thank the KINARM technologists, Ms. Simone Appaqaq, Ms. Kim Moore, and Ms. Helen Bretzke.

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

pCO_2: Arterial Partial Pressure of Carbon Dioxide

PICS: Post-intensive Care Syndrome

pO_2: Arterial Partial Pressure of Oxygen

RASS: Richmond Agitation and Sedation Scale

RBANS: Repeatable Battery for the Assessment of Neuropsychological Status

rSO_2: Regional Cerebral Oxygenation

RVGR: Reverse Visually Guided Reaching

SpO_2: Peripheral Oxygen Saturation

SS: Spatial Span

SDM: Substitute Decision Maker

VGR: Visually Guided Reaching

Authors' contributions:

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

JK participated in study design and drafting of the manuscript.

KL participated in study design and drafting of the manuscript.

DM participated in study design and drafting of the manuscript.

JM participated in study design and drafting of the manuscript.

MH participated in study design and drafting of the manuscript.

SHS participated in study design and drafting of the manuscript.

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

JAJ participated in statistical planning and drafting of the manuscript.

IB participated in study design and drafting of the manuscript.

MS participated in study design and drafting of the manuscript.

NO participated in study design and drafting of the manuscript.

SE participated in study design and drafting of the manuscript.

VM participated in study design and drafting of the manuscript.

MC participated in study design and drafting of the manuscript.

DG participated in study design and drafting of the manuscript.

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

Funding statement:

This work was supported by the Physician Services Incorporated and the Southeastern Ontario Academic Medical Organization New Clinician Scientist Program for which JGB was the

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

Competing interests statement.

Mr. Michael D. Wood has nothing to disclose.

Ms. Jasmine Khan has nothing to disclose.

Dr. Kevin Lee has nothing to disclose.

Dr. David Maslove has nothing to disclose.

Dr. John Muscedere is the scientific director of the Canadian Frailty Network.

Ms. Miranda Hunt has nothing to disclose.

Dr. Stephen Scott is the cofounder of BKIN Technologies, the manufacturer of the KINARM device.

Mr. Andrew Day has nothing to disclose.

Dr. Jill Jacobson has nothing to disclose.

Dr. Ian Ball receives a stipend from the Trillium Gift of Life Network to support his role as a Regional Medical Lead.

Dr. Niamh O'Regan received funding from the Academic Medical Organization of Southwestern Ontario.

Dr. Marat Slessarev receives a stipend from the Trillium Gift of Life Network to support his role as a Hospital Donation Physician.

Dr. Victoria McCredie has nothing to disclose.

Dr. Shane English has nothing to disclose.

Dr. Donald Griesdale is funded through a Health-Professional Investigator Award from the Michael Smith Foundation for Health Research.

Dr. J. Gordon Boyd receives a stipend from the Trillium Gift of Life Network to support his role as a Regional Medical Lead.

Figure Legends:

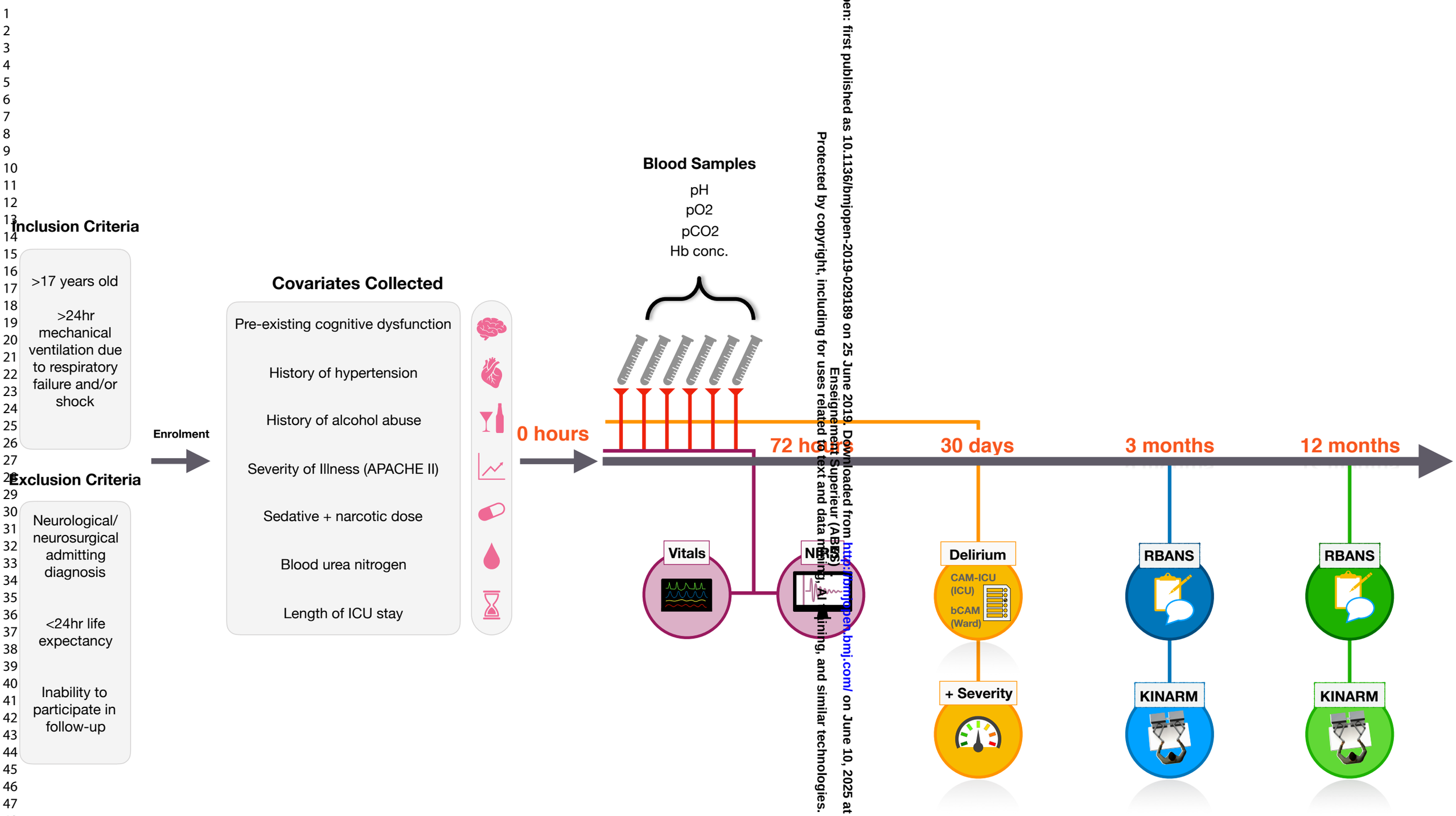
Figure 1. A visual representation of the CONFOCAL2 study design from enrolment to 3- and 12-month follow up assessments.

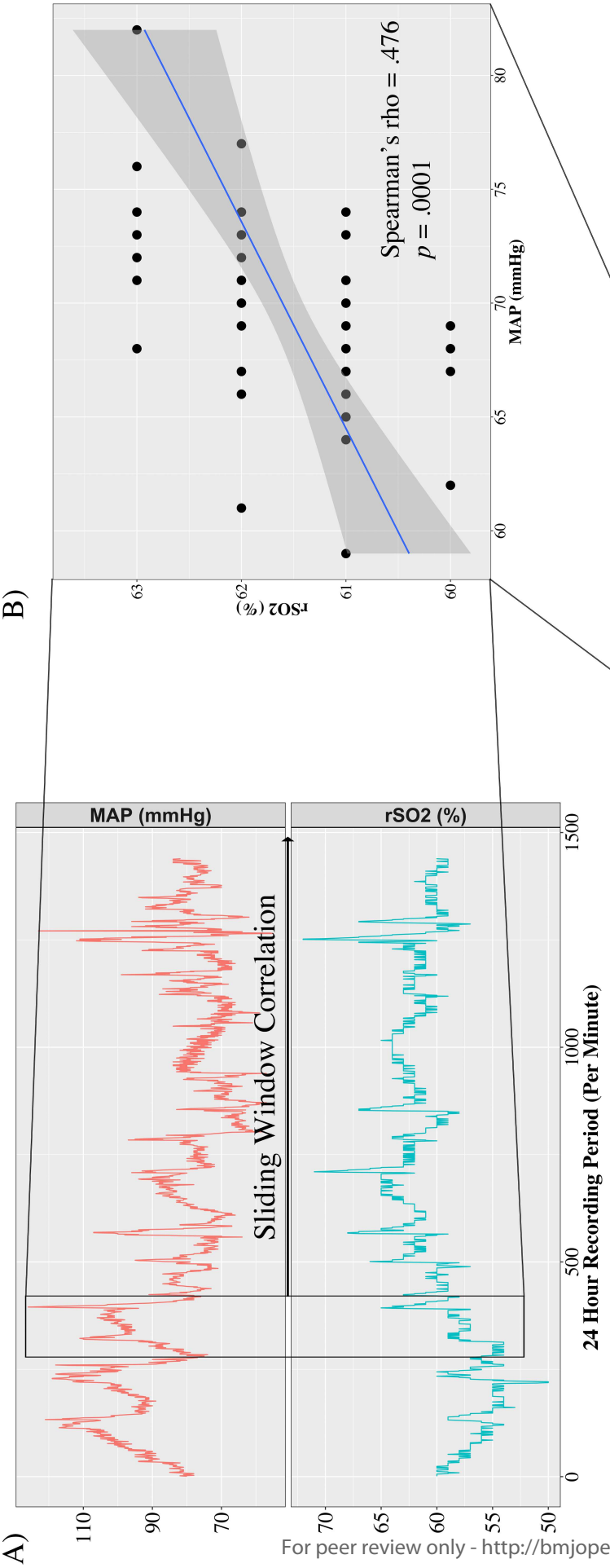
Figure 2. Three-dimensional animated representation of the KINARM End-Point robotic set-up used at 3- and 12-month follow up assessments.

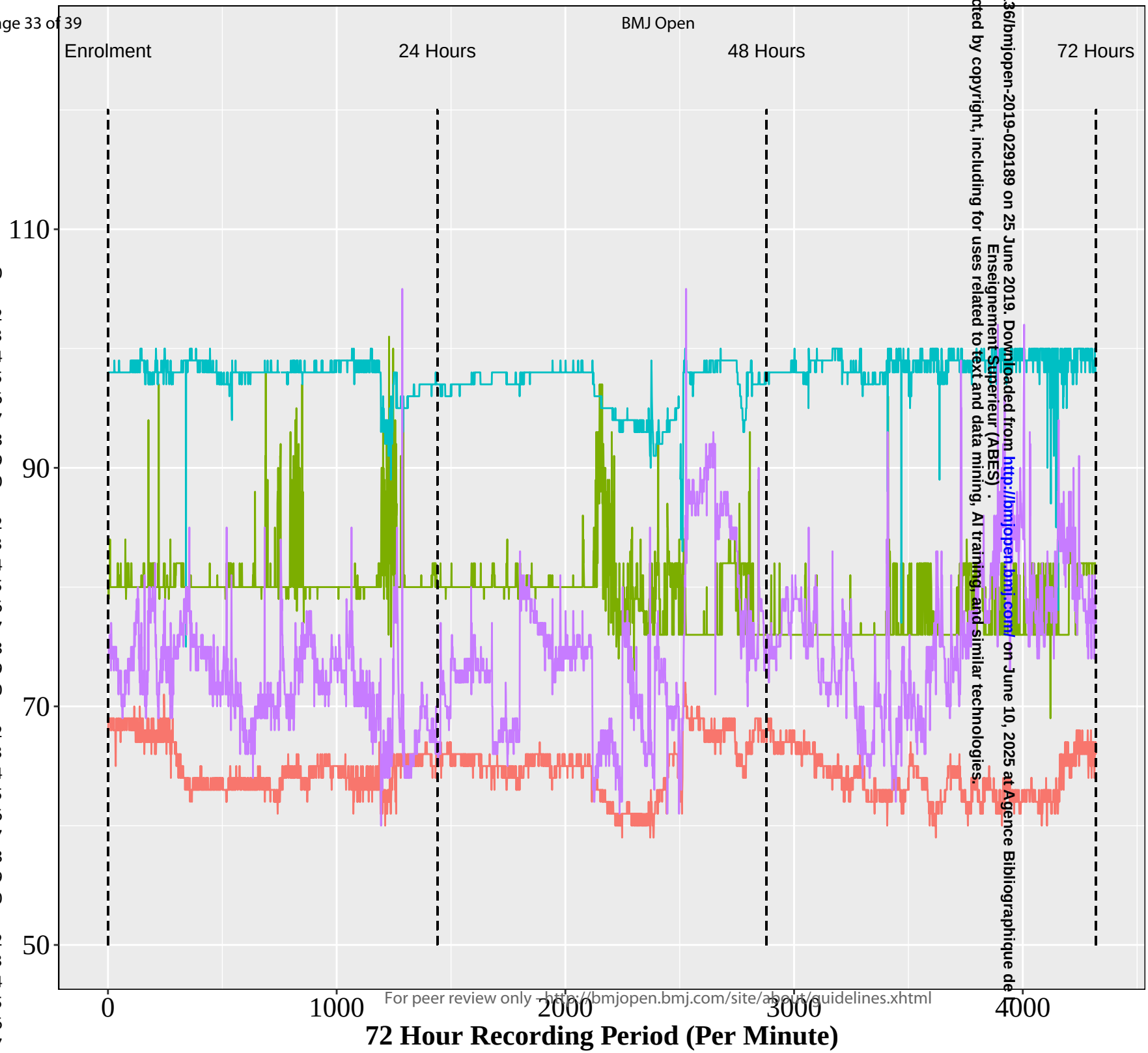
Figure 3A. Simplified line graph (24 hours instead of the full 72 hour recording period) illustrating the sliding window correlation between mean arterial pressure and regional cerebral oxygenation for an individual patient over a 24 period of recording. *Note*. The black rectangle represents a 60-minute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

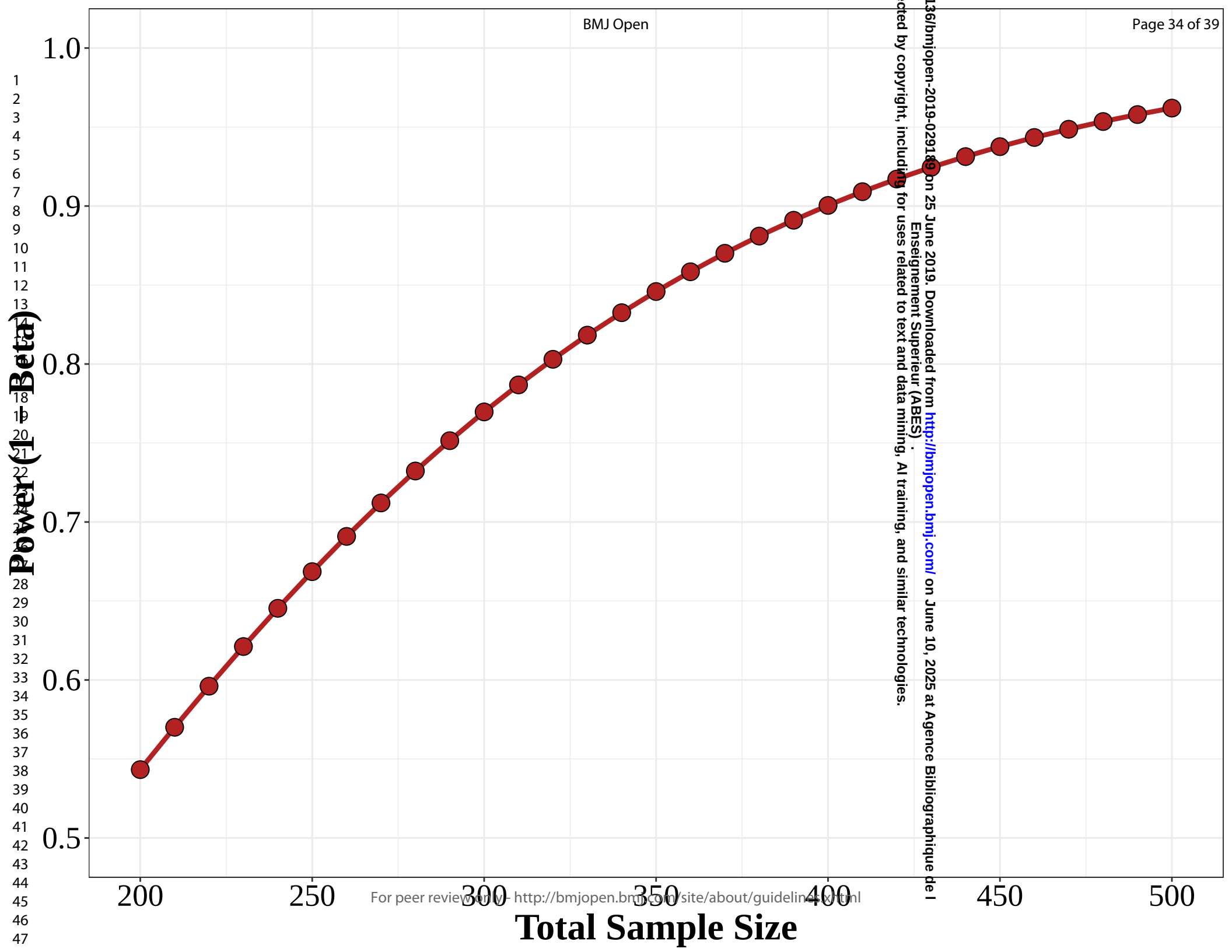
Figure 4. Line graph of the high frequency vital sign recordings indicates the highly variable relationships with regional cerebral oxygenation over the 72-hour period of recording. *Note*. The figure represents a single patient's ICU recording. rSO_2 = Regional cerebral oxygenation; HR = Heart rate; SpO_2 = Arterial oxygen saturation; artMAP= Mean arterial pressure from an arterial line.

Figure 5. A power curve indicating the study sample size, and the respective statistical power, to asses the primary study outcome. *Note.* Red dots represent the sample size needed for a given statistical power. The primary sample size was calculated using the following multivariate regression model parameters: 10 independent variables tested, controlling for 9 additional covariates, power = 0.90, $R^2 = 0.050$, $\alpha = 0.05$, which would require a sample size of 400.









SPIRIT
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			

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
	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
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
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
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15-18
	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
Methods: Monitoring			
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
	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:	*BMJ Open*
Manuscript ID	bmjopen-2019-029189.R2
Article Type:	Protocol
Date Submitted by the Author:	24-May-2019
Complete List of Authors:	Wood, Michael; Queen's University, Centre For Neuroscience Studies Khan, Jasmine; Queen's University, Centre for Neuroscience Studies Lee, Kevin; Queen's Univeristy, School of Medicine Maslove, David M; Queen's University , Critical Care Medicine Muscedere, John; Kingston General Hospital, Critical Care Medicine Hunt, Miranda; Queen's University, Critical Care Medicine Scott, Stephen; Queen's University, Centre for Neuroscience Studies Day, Andrew ; Queen's Unversity, Department of Community health and Epidemiology and CERU Jacobson, Jill; Queen's University, Psychology Ball, Ian; London Health Sciences Centre, Medicine Slessarev, Marat; Western University, Medicine, Division of Geriatric Medicine O'Regan, Niamh; Western University, Medicine, Division of Geriatric Medicine English, Shane; University of Ottawa, Medicine (Critical Care); Ottawa Hospital Research Institute, Clinical Epidemiology Program McCredie, Victoria; University of Toronto; Toronto Western Hospital, University Health Network, Medicine; Critical Care Chasse, Michaël; Centre Hospitalier de L'Universite de Montreal, Medicine (Critical Care) Griesdale, Donald; University of British Columbia, Department of Anesthesiology, Pharmacology & Therapeutics Boyd, John; Kingston General Hospital, Critical Care Medicine
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.

Supplemental Figure 1.gif

Title: 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

Authors: The Cerebral Oxygenation and Neurological Outcomes Following Critical Illness (CONFOCAL) Research Group

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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 (rSO_2) to assess the association between poor rSO_2 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 rSO_2 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, rSO_2 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

peer review. Results will also be presented at national/international scientific conferences. Upon completion, the study findings will be submitted for publication in peer-reviewed journals.

Trial Registration: This trial is registered on clinicaltrials.gov (Identifier: NCT03141619), registered May 5, 2017.

Key Words: Near-infrared spectroscopy; Cerebral oximetry; Cerebral autoregulation; KINARM, Delirium; CAM-ICU; Post-intensive care syndrome; RBANS

Strengths and Limitations of this study:

- CONFOCAL2 will further assess the association between poor regional cerebral oxygenation (rSO_2) and delirium, as well as long-term cognitive outcomes among survivors.
- Although this study is observational in nature, which limits causal inferences, broad inclusion criteria and a representative sample size will increase external validity of our findings.
- CONFOCAL2 closely resembles routine clinical practice with only minor methodological differences (e.g., rSO_2 monitoring) and results will have the potential to directly translate into clinical practice.

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 known as the KINARM, which uses the participant's upper limbs to asses sensorimotor and cognitive function,has indicated that ICU survivors also develop visuospatial and motor deficits.[9] Importantly, when assessed using the Repeatable Battery for Neuropsychological Status (RBANS), many critical illness survivors had performance scores 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.

This issue has resulted in a limited number of studies investigating the influence of cerebral perfusion on delirium in critically ill patients (Reviewed in[11]). Near-infrared spectroscopy (NIRS) is a non-invasive technology that measures regional cerebral oxygenation (rSO_2) as a surrogate marker of cerebral perfusion,[12,13] as rSO_2 values correlate with other markers of cerebral perfusion, including CT perfusion, jugular venous bulb oxygen saturation, and brain tissue oxygen tension.[12–14] Therefore, NIRS is an ideal candidate for both ICU research and clinical practice.

Feasibility and single-center prospective ICU studies have been performed with NIRS, discovering that low rSO_2 is an independent risk factor for the development of delirium.[15,16] A nested cohort in this study demonstrated that impaired cerebral auto-regulation (i.e., the ability to maintain stabilized and adequate cerebral perfusion) is also associated with the development and duration of delirium.[17,18] While these findings were statistically significant, a multi-centre observational study is necessary for external validation and the study of long-term outcomes.

Our overarching hypothesis is that decreased rSO_2 in the early stages of critical illness leads to the development of delirium, as well as long-term cognitive impairment among survivors. The primary objective is to further establish an association between poor cerebral perfusion and delirium severity. Secondary objectives include assessing the hemodynamic and physiological determinants of rSO_2, as well as to identify potential risk factors (e.g., poor rSO_2) associated with delirium and long-term cognitive deficits. Overall, elucidating the mechanisms of acute and chronic neurological impairment will allow for the development of preventative 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 5 sites within Ontario, 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 study[16] 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,

neuromuscular disorders). Post-cardiac arrest patients are also excluded from this study. Additional study sites will include the following: London Health Sciences Centre-Victoria Hospital (London, ON; Site PI Dr. Ian Ball, with co-PIs Dr. Marat Slesserev and Dr. Niamh O'Reagan), Ottawa General Hospital (Site PI Dr. Shane English), and Ottawa Civic Hospital (Site PI Dr. Shane English). KHSC is responsible for developing and maintaining the electronic case report forms (eCRF), data management, and analysis.

Potential non-Ontario site expansion: We are anticipating an enrolment rate of 1-2 patients per site/month. Should our enrolment rates be slower than anticipated, additional sites have already agreed to participate in this study, including: Toronto Western Hospital (Site PI Dr. Victoria McCredie, Université de Montreal (Montreal, QC; Site PI Dr. Michael Chasse) and Vancouver General Hospital (Site PI Dr. Donald Griesdale). Local Ethics approval would be sought prior to enrolment in this study.

Recruitment and consent: The Queen's University and Affiliated Hospitals Health Sciences Research Ethics Board will serve as the board of record for the streamlined research ethics review system (Clinical Trials Ontario) and all Ontario sites have gained approval; Non-Ontario sites will need to obtain local ethics approval at their earliest convenience. All patients admitted to the ICU will be screened daily for eligibility. The participant will be approached by a member of the research staff. If the participant is unable to provide consent, the research staff will approach the Substitute Decision Maker (SDM). The research coordinator or trained study staff will obtain informed consent and documentation of the consent process will be noted in the patient's medical chart. As patients meeting eligibility criteria are unlikely to be able to give

informed consent at the time of enrolment due to their critical condition, we will employ a deferred consent model when appropriate (e.g., SDMs are frequently in an emotional state and may not be available to be contacted), which has already been granted local research ethics board approval. When an SDM is not available to approach, we will enrol the patient and begin trial procedures until the SDM is available for a consent encounter, targeted to be within 72 hours of enrolment. However, we will encourage an *a priori* informed consent whenever possible. The SDM response will be used to continue all trial procedures or any further data collection. If the patient or substitute decision maker declines enrolment, then the patient will be excluded, and all data obtained using deferred consent will be confidentially destroyed. In addition, once the patient has regained capacity according to the medical team, the patient will be approached to affirm or withdraw consent. Each site will be provided with patient identification numbers, which will be assigned sequentially when a patient is enrolled and will be used in all study documentation to ensure patient confidentially and anonymity. All eligible patients will be recorded on a screening log, which will include their study ID, date of consent, or reason the patient could not be enrolled. The de-identified screening log will be forwarded to the lead project coordinator on a monthly basis. The individual site research coordinators and investigators will be responsible for ensuring the ethical conduct of this trial, screening patients, obtaining consent, and training of staff as needed. The principal investigators and co-investigators will review monthly compliance with the study protocol and recruitment rates.

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

will be destroyed. In accordance with current requirements, we will store the de-identified data for a minimum of 10 years.

Data Collection:

rSO_2, hemodynamics, medications, and clinical characteristics: Patients will be enrolled within the first 24 hours of their ICU admission. Immediately following enrolment, the patient will undergo rSO_2 monitoring. A sensor will be placed in the centre of the patient's forehead, which is attached to the FORESIGHT ELITE oximeter (CASMED, Caster Medical, Canada). This device will provide continuous quantification of rSO_2, every 2 seconds, for 72 hours. To assess the association between hemodynamics and rSO_2 recordings, we will use a commercially available system (Bedmaster, Excel Medical Electronics, FL, USA; or site equivalent) to capture the following vital signs from enrolled patients: heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and peripheral oxygen saturation (SpO_2). These data are captured locally and uploaded to the eCRF (REDCap). Throughout this 72-hour period of recording, we will document adminstered continuous infusion and intermittent bolus doses of vasoactive and sedative/analgesic medications, which will be converted to either "fentanyl equivalents" for narcotics, or "midazolam equivalents" for benzodiazepine medications. These conversion formulas have been previously described.[19] Severity of illness will be measured during the first 24 hours of ICU admission using the Acute Physiology and Chronic Health Evaluation II score (APACHE II). Trained research staff will approach whomever provided informed consent (i.e., either the patient or the SDM) to ascertain the enrolled patient's pre-existing frailty (i.e., prior to ICU admission) using the clinical frailty scale,[20] which is 9-point scale (e.g., 1 = very fit to 9 = terminally ill). All clinical data will be captured on the eCRF.

Central venous and arterial blood collection: Both arterial and central venous gases will be sampled every 12 hours during the 72h period of rSO_2 recording and will include: pH, partial pressure of oxygen (pO_2), partial pressure of carbon dioxide (pCO_2), and hemoglobin concentration (Hb). These blood samples will be collected only if a central line (PICC, internal jugular, subclavian) and arterial line are *already* in place.

Delirium screening: Patients will be assessed once daily for deliriumthroughout their entire hospital stay (ICU and ward; up to day 30) using validated screening tools; the Confusion Assessment Method (CAM)-ICU[21], as well as the brief Confusion Assessment Method (bCAM)[22] which will be administered on the ward. Both delirium screening tools will be administered by trained research staff at a time that is convenient for the patient, their family, and the medical team directing their care.

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

Determination of pre-existing cognitive impairment: Our pilot study[16] excluded 10% of patients with a documented history of cognitive impairment in their medical chart, which may limit external validity. Importantly, individuals may have substantial cognitive impairment prior to enrolment but did not receive any formal diagnosis. To address this potential confound, all patients will be assessed, upon enrolment, using the clinical dementia rating (CDR) scale.[24] The CDR is a scale from 0 (Normal) to 3 (severe dementia) that is calculated from a standardized scoring sheet completed by interviewing a patient or their caregiver. All staff completing the

interview and scoring sheet will undergo rigorous online training and pass a certification exam. A diagnosis of pre-existing cognitive impairment will be defined as a CDR >1.

3- and 12-Month Follow Up:

Neuropsychological assessment: Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): Participants will complete a 3- and 12-month follow up assessment in which the RBANS will be administered by a trained researcher. The RBANS assesses global cognition, as well as several subdomains (i.e., immediate and delayed memory, visuospatial/constructional, language, and attention). These indices have been described previously,[25] and survivors will be compared to age-matched controls. To improve follow up rates, in home/hospital testing will be performed for individuals not able to return for laboratory assessment. Participant scores are converted to standardized values in which the normative range will be considered a mean of 100+/-24.75 (1.65 SD). Participants that score >75 will not be considered impaired, as these subjects are performing within or above the normative range. The RBANS assessment requires ~20-30 minutes to complete.

KINARM Assessment: Participants (from the Kingston region only) will complete a 3- and 12-month follow up assessment using the End-Point bimanual KINARM robot (BKIN Technologies, Kingston). With each hand, the seated subject grasps a handle attached to a planar robotic device that permits movements in the horizontal plane with an integrated virtual reality system that presents objects in the horizontal plane (Figure 2). Subjects will perform a behavioural battery to quantify a broad range of sensorimotor, and cognitive function using their upper limbs. A trained operator selects a task from the software menu, reads the standardized

instructions, and then monitors performance in real-time. We will administer 8 tasks from the KINARM Standard Tests™ including: Object Hit (OH),[26] Object Hit and Avoid (OHA),[27] Ball on Bar (BonB),[28] Visually Guided Reaching (VGR),[29] Reverse Visually Guided Reaching (RVGR),[30] Spatial Span (SS), Trail Making A and B, and Arm Position Matching (APM),[31]. Each task has been previously described,[32]and quantifies subject performance using approximately 6 to 12 metrics per task. Each metric is converted into normalized units based on healthy subject performance, considering the influence of sex, age, and handedness (0 is mean performance and ±1 is a standard deviation from the mean). For each task, a task score will also be generated to provide a global performance measure with values that are equivalent to standard deviation units with zero specifying best possible performance, and higher values indicating worse performance. Therefore, performance will be considered abnormal if the task score is outside the +1.96 range (i.e., 5th percentile). The task score has been previously described.[33] The KINARM assessment takes ~45 minutes to complete.

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 described[18] and a visual representation can be observed in Figure 3. 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. However, we will define cerebral autoregulation dysfunction by using a statistical significance threshold for positive COx correlation values ($p<0.0001$). Cumulative duration of disturbed autoregulation will be given by the duration of time spent with a significant positive correlation throughout the period of neuromonitoring. Computer algorithms for COx will be developed and implemented blind to the neurological status of enrolled patients.

Estimating optimal MAP: To calculate the individualized optimal MAP (MAP_{OPT}), the computed COx values will be binned by the average MAP value in their respective moving windows in 5 mmHg bins.[34] An alternative strategy will also be implemented. We will invert the MAP_{OPT} binning procedure by binning MAP values by their corresponding COx values in sequential 0.05 bins of Spearman correlation coefficients ranging from -1 to +1. This procedure has been previously described.[18]

Assessment of primary outcome: Multivariate linear regression will be used to characterize the association between adequate cerebral perfusion (as measured using duration of time (minutes) outside of MAP_{OPT}, mean rSO_2, and duration of disturbed cerebral autoregulation) and delirium severity throughout a patient's ICU stay to determine if poor cerebral oxygenation is an independent predictor of delirium. We will estimate the unadjusted effect of each individual predictor on delirium severity (i.e., cumulative CAM-7 scores per patient). The simultaneous multivariate regression model will adjust for the following covariates due to their potential associations with delirium: a history of hypertension, a history of alcohol abuse, total sedative dose (in midazolam equivalents), total narcotic dose (in fentanyl equivalents), severity of illness (APACHE II scores), pre-existing cognitive impairment (CDR score), length of ICU stay, frailty,

(clinical frailty scale) and blood urea nitrogen. The multivariable model will provide the adjusted regression coefficients after controlling for all predictors included in the model. All covariates included in regression modeling have been chosen *a priori* based on clinical judgment and previous research.[16,35] Model diagnostics will be conducted to assess the underlying assumptions of linear regression (i.e., linearity, normally distributed residuals, equal variances, and lack of multicolinearity) for all models. Multiple imputation strategies will be applied at the time of the regression modeling to account for any missing data and reduce bias associated with excluding patients due to partially collected data.

Secondary outcomes:

Determinants of rSO_2: To assess the hemodynamic and physiological determinants of rSO_2 at the patient level, multiple linear regression will be performed using the patient average of each variable over the 72-hour data collection period. The following predictors will be included in the regression model: HR, SpO_2, MAP, arterial, and venous blood gas data (i.e., pH, pO_2, and pCO_2), central venous oxygen saturation, and Hb concentration. In addition, the multivariate model will control for the following covariates associated with cerebral perfusion: age,[36] as well as total sedative, narcotic, and vasopressor dosing. Simultaneous multiple linear regression with adjustment for all aforementioned covariates will be implemented. As stated for the primary outcome regression analysis, model diagnostics will be performed. Furthermore, the relationship between the determinants of the NIRS-derived rSO_2 signal may vary over time (see Figure 4 and Supplemental Movie 1). Therefore, a repeated measures analysis will also be performed by using multilevel modeling with 6 observations reflecting each 12-hour period during the 72-hour data collection period (with time coded as 0 – 5, so the intercept equals baseline/time of enrolment) nested within each subject. The predictors will be the same as the regression model but allowed

to be time varying across the 6 observation points. This analysis will assess if within patient changes in the predictors correlate with changes in rSO_2, and if these associations are modified by fixed patient characteristics, such as age.

Assessing if poor cerebral perfusion during critical illness is a significant predictor of long-term neurological dysfunction among ICU survivors: Multiple linear regression analysis will be used to assess if impaired cerebral perfusion (i.e., time below MAP_{OPT}, mean rSO_2, and duration of disturbed cerebral autoregulation) is associated with RBANS global cognition scores at 3- and 12-months post-ICU discharge. We will use the following clinical covariates collected on admission (i.e., pre-existing cognitive impairment, age, severity of illness, frailty) and data collected within the first 72 hours of the patients' ICU stay (i.e., narcotic dosing and benzodiazepine dosing). All covariates will be adjusted for in separate regression models for the cognitive outcomes at 3- and 12-months post-ICU discharge. If global cognition is significantly predicted by the time below MAP_{OPT}, we will conduct an exploratory analysis of the RBANS subdomains of cognition (i.e., delay and immediate memory, language, attention, visuospatial/constructional) adjusting for the aforementioned covariates to further explore specific areas of impairment observed among survivors of critical illness. Due to the limited availability of the KINARM robot across sites, only patients assessed at KHSC will undergo KINARM testing.This data will be assessed with descriptive statistics only to avoid any potential bias introduced by this design.

Sample Size Calculation:

Primary Outcome: Our overall hypothesis is that poor cerebral perfusion contributes to delirium and long-term cognitive impairment. For study purposes, we define poor cerebral perfusion as the composite of 1) low mean rSO_2, 2) duration of impaired cerebral autoregulation, and 3) time

outside individualized optimal MAP (MAP_{OPT}), which will be discussed in more detail in the statistical plan section. We acknowledge that this in an imperfect measure of cerebral perfusion. However, this is a comprehensive, continuous, and non-invasive assessment of cerebral perfusion. For our primary outcome (CAM-7 delirium severity score), we will enrol a total of 500 patients, as our prior work has demonstrated that ~20% of patients remain comatose (RASS = -4 or -5) during their entire ICU stay[16], and cannot be assessed for delirium. Therefore, using our pilot data, we estimate that ~100 patients will be remain comatose resulting in approximately 400 patients to assess our primary outcome, which will allow for 10 degrees of freedom for our 3 measures of perfusion (i.e., mean rSO_2, duration of disturbed cerebral autoregulation, duration outside MAP_{OPT}) and controlling for the 9 covariates (see below). The 10 degrees of freedom will allow us to model non-linear relationships between the 3 measures of cerebral perfusion and delirium severity. This sample size achieves 90% power to detect an R^2 of 0.050 collectively among these measures of cerebral perfusion and using an F-test with a significance level (alpha) of 0.050 (see Figure 5).

Secondary Outcomes-Physiological determinants of rSO_2 and neurological outcomes

For evaluating the determinants of the rSO_2 signal during critical illness, we will assess the association between each of the 9 pre-specified candidate predictors of rSO_2 after controlling for the 4 co-variates (see below for co-variates). We will use a Bonferroni correction (0.05/9=0.0056) to control for multiple testing. With the total 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. However, our pilot data indicated a 30% mortality rate. Given our overall sample size of 500 patients recruited, we are anticipating ~350 ICU survivors (i.e., 500-150) to return for follow up assessment. This cohort will provide sufficient power to detect important predictors of long-term neurological outcomes. However, these predictors have been intentionally not specified *a priori*, as this analysis will be dependent on our findings related to cerebral perfusion and delirium.

All sample size calculations were conducted using Power Analysis and Sample Size Software (Version 15).[37]

The actual start date at KHSC began on January 26, 2018 and our estimated primary completion data is June 2022. Due to our 12 month follow up, we expect the study to be completed June 2023.

DISCUSSION

This multicentre observational study will extend our preliminary findings of reduced rSO_2 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 rSO_2 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 rSO_2. It will lay the foundation for a larger interventional study designed to assess whether optimization of rSO_2 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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Acknowledgments:

The authors would like to thank the study coordinators, Ms. Miranda Hunt, Ms. Ilinca Georgescu, and Mrs. Tracy Boyd, as well as the entire KHSC ICU staff for their continued support of our clinical research. This manuscript underwent an internal peer-review process with the Canadian Critical Care Trials Group, and we are greatly appreciative of the helpful contributions made by both Dr. Lisa Burry and Dr. Pierre Cardinal. We would also like to thank the KINARM technologists, Ms. Simone Appaqaq, Ms. Kim Moore, and Ms. Helen Bretzke.

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

pCO_2: Arterial Partial Pressure of Carbon Dioxide

PICS: Post-intensive Care Syndrome

pO_2: Arterial Partial Pressure of Oxygen

RASS: Richmond Agitation and Sedation Scale

RBANS: Repeatable Battery for the Assessment of Neuropsychological Status

rSO_2: Regional Cerebral Oxygenation

RVGR: Reverse Visually Guided Reaching

SpO_2: Peripheral Oxygen Saturation

SS: Spatial Span

SDM: Substitute Decision Maker

VGR: Visually Guided Reaching

Authors' contributions:

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

JK participated in study design and drafting of the manuscript.

KL participated in study design and drafting of the manuscript.

DM participated in study design and drafting of the manuscript.

JM participated in study design and drafting of the manuscript.

MH participated in study design and drafting of the manuscript.

SHS participated in study design and drafting of the manuscript.

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

JAJ participated in statistical planning and drafting of the manuscript.

IB participated in study design and drafting of the manuscript.

MS participated in study design and drafting of the manuscript.

NO participated in study design and drafting of the manuscript.

SE participated in study design and drafting of the manuscript.

VM participated in study design and drafting of the manuscript.

MC participated in study design and drafting of the manuscript.

DG participated in study design and drafting of the manuscript.

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

Funding statement:

This work was supported by the Physician Services Incorporated and the Southeastern Ontario Academic Medical Organization New Clinician Scientist Program for which JGB was the

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

Competing interests statement.

Mr. Michael D. Wood has nothing to disclose.

Ms. Jasmine Khan has nothing to disclose.

Dr. Kevin Lee has nothing to disclose.

Dr. David Maslove has nothing to disclose.

Dr. John Muscedere is the scientific director of the Canadian Frailty Network.

Ms. Miranda Hunt has nothing to disclose.

Dr. Stephen Scott is the cofounder of BKIN Technologies, the manufacturer of the KINARM device.

Mr. Andrew Day has nothing to disclose.

Dr. Jill Jacobson has nothing to disclose.

Dr. Ian Ball receives a stipend from the Trillium Gift of Life Network to support his role as a Regional Medical Lead.

Dr. Niamh O'Regan received funding from the Academic Medical Organization of Southwestern Ontario.

Dr. Marat Slessarev receives a stipend from the Trillium Gift of Life Network to support his role as a Hospital Donation Physician.

Dr. Victoria McCredie has nothing to disclose.

Dr. Shane English has nothing to disclose.

Dr. Donald Griesdale is funded through a Health-Professional Investigator Award from the Michael Smith Foundation for Health Research.

Dr. J. Gordon Boyd receives a stipend from the Trillium Gift of Life Network to support his role as a Regional Medical Lead.

Figure Legends:

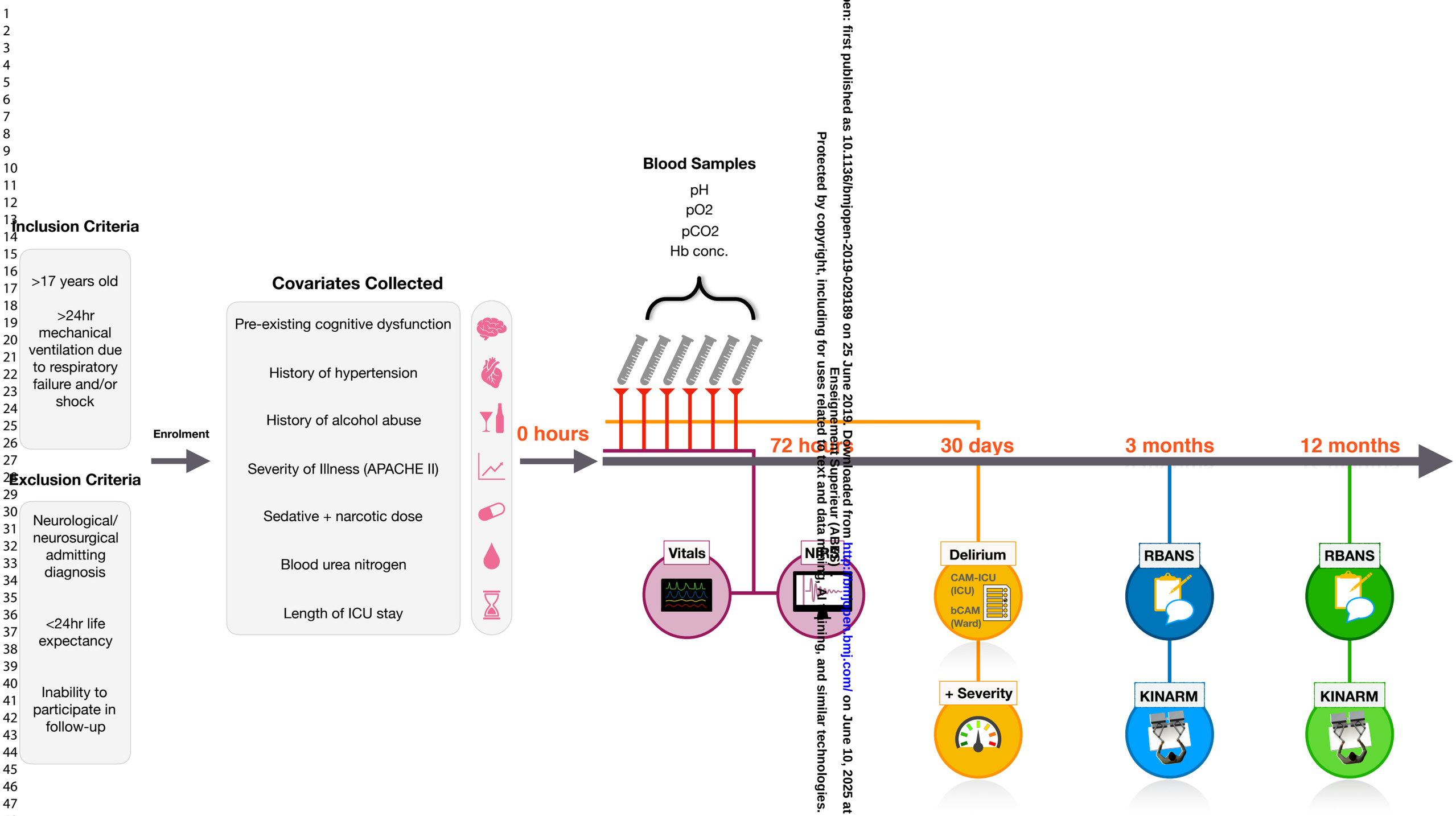
Figure 1. A visual representation of the CONFOCAL2 study design from enrolment to 3- and 12-month follow up assessments.

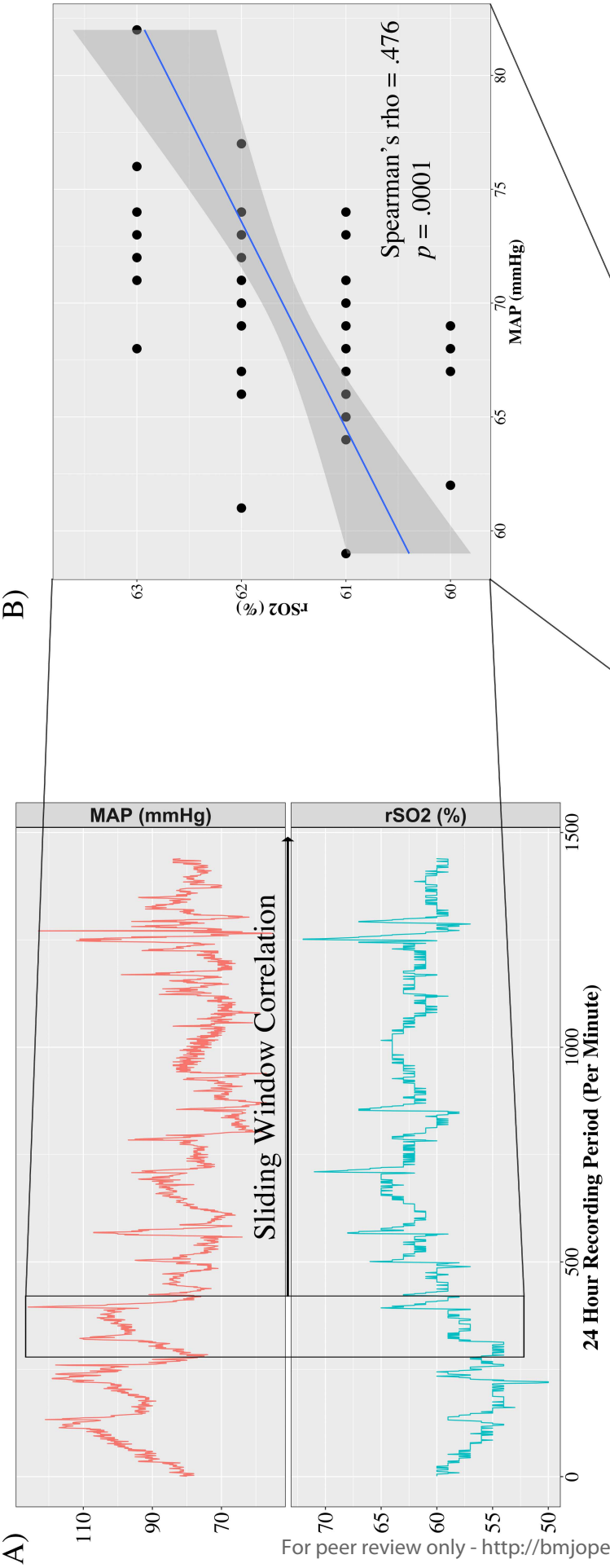
Figure 2. Three-dimensional animated representation of the KINARM End-Point robotic set-up used at 3- and 12-month follow up assessments.

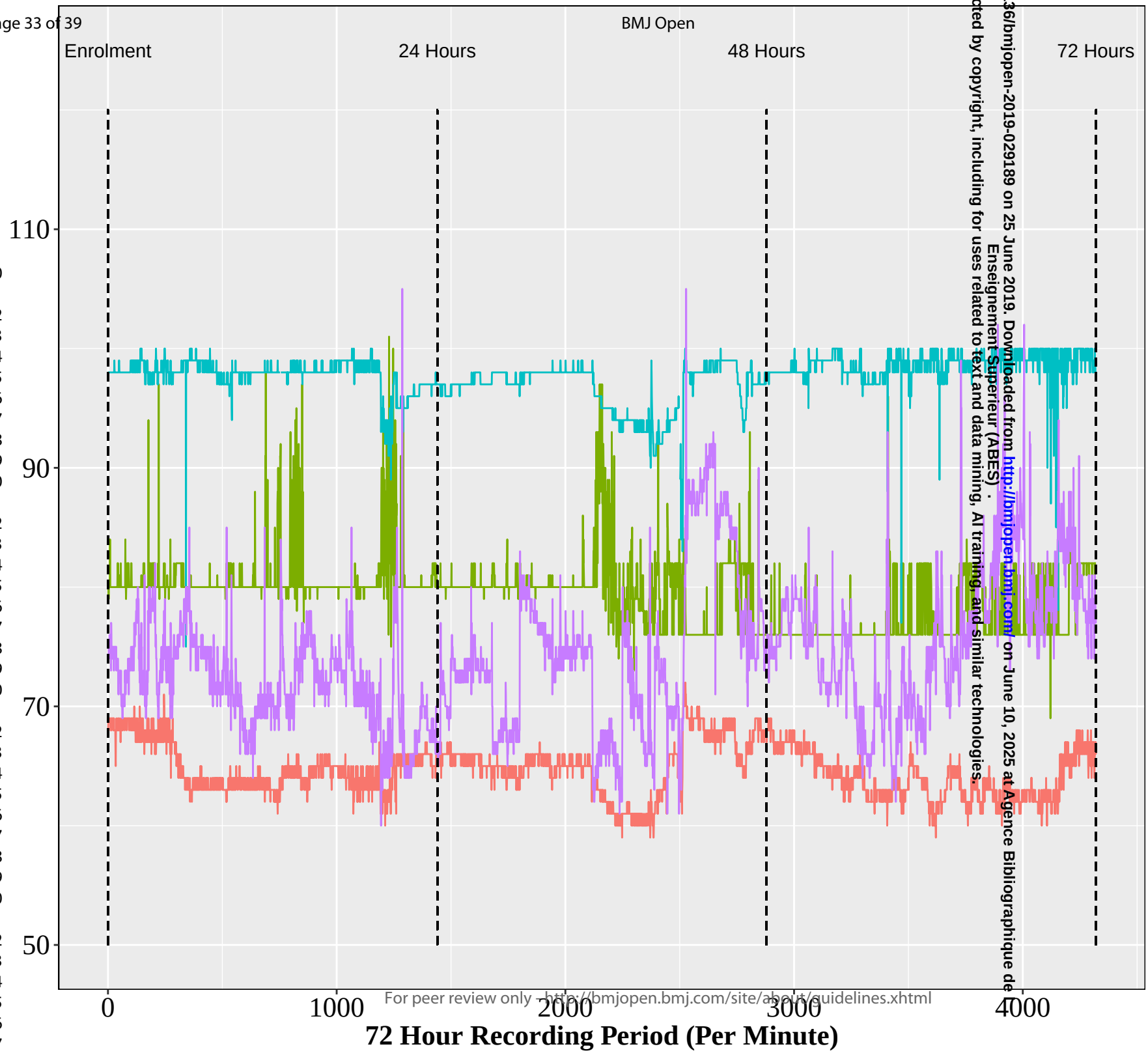
Figure 3A. Simplified line graph (24 hours instead of the full 72 hour recording period) illustrating the sliding window correlation between mean arterial pressure and regional cerebral oxygenation for an individual patient over a 24 period of recording. *Note*. The black rectangle represents a 60-minute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

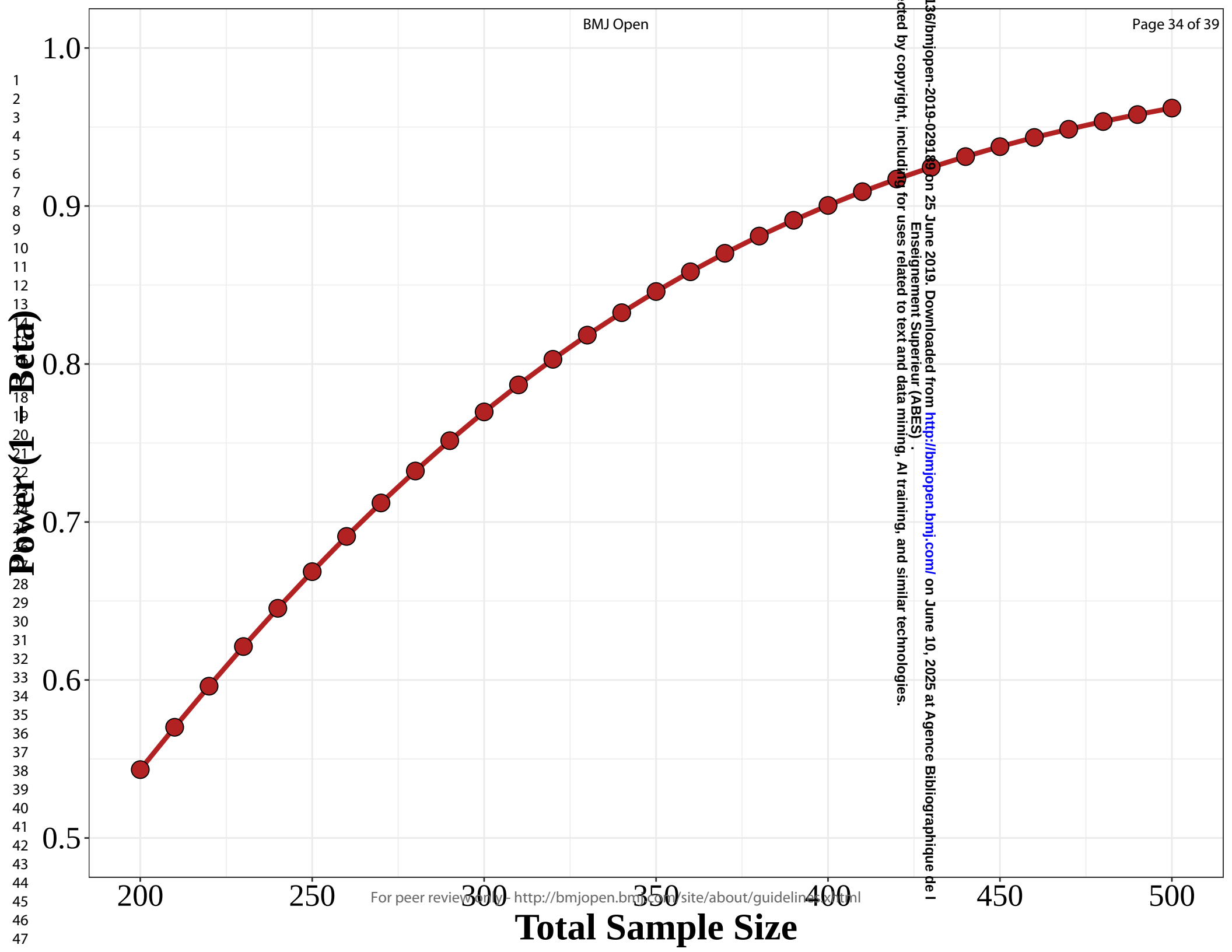
Figure 4. Line graph of the high frequency vital sign recordings indicates the highly variable relationships with regional cerebral oxygenation over the 72-hour period of recording. *Note*. The figure represents a single patient's ICU recording. rSO_2 = Regional cerebral oxygenation; HR = Heart rate; SpO_2 = Arterial oxygen saturation; artMAP= Mean arterial pressure from an arterial line.

Figure 5. A power curve indicating the study sample size, and the respective statistical power, to asses the primary study outcome. *Note.* Red dots represent the sample size needed for a given statistical power. The primary sample size was calculated using the following multivariate regression model parameters: 10 independent variables tested, controlling for 9 additional covariates, power = 0.90, $R^2 = 0.050$, $\alpha = 0.05$, which would require a sample size of 400.









SPIRIT
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			

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
	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
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
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
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15-18
	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
Methods: Monitoring			
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
	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.