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Identifying neurocognitive outcomes and cerebral oxygenation in critically ill adults on acute kidney replacement therapy in the intensive care unit: The INCOGNITO-AKI study protocol

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Title: Identifying neurocognitive outcomes and cerebral oxygenation in critically ill adults on acute kidney replacement therapy in the intensive care unit: The INCOGNITO-AKI study protocol

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ABSTRACT

Introduction. Initiation of acute kidney replacement therapy (KRT) is common in critically ill adults admitted to the intensive care unit (ICU), and associated with increased morbidity and mortality. KRT has been linked to poor neurocognitive outcomes, leading to reduced quality of life, and increased utilization of healthcare resources. Adults on dialysis in the ICU may be particularly at risk of neurocognitive impairment, as survivors of critical illness are already predisposed to developing cerebrovascular disease and cognitive dysfunction long-term relative to healthy controls. Regional cerebral oxygen saturation (rSO₂) may provide a critical early marker of long-term neurocognitive impairment in this population. This study aims to understand cerebral oxygenation in patients undergoing KRT (continuous or intermittent) in the ICU. These findings will be correlated with long-term cognitive and functional outcomes, and structural brain pathology.

Methods and analysis. 108 patients scheduled to undergo treatment for acute kidney injury with KRT in the Kingston Health Sciences Centre ICU will be recruited into this prospective observational study. Enrolled patients will be assessed with intradialytic cerebral oximetry using near infrared spectroscopy (NIRS). Delirium will be assessed daily with the Confusion Assessment Method-Intensive Care Unit (CAM-ICU) and severity quantified as cumulative CAM-ICU-7 scores. Neurocognitive impairment will be assessed at 3- and 12-months after hospital discharge using the Kinarm and Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). Structural brain pathology on MRI will also be measured at the same timepoints. Driving safety, adverse events, and medication adherence will be

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assessed at 12-months to evaluate the impact of neurocognitive impairment on functional outcomes.

Ethics and dissemination. This study is approved by the Queen’s University Health Sciences/Affiliated Teaching Hospitals Research Ethics Board (DMED-2424-20). Results will be presented at critical care conferences, and a lay summary will be provided to patients in their preferred format.

Trial registration number. Pending.

ARTICLE SUMMARY

Strengths and limitations of this study:

- This will be the first study to use a comprehensive battery of neurological tests to interrogate both short- and long-term neurological impairment in critically ill adults on dialysis
- This study will employ robotic technology in a novel patient population to provide a quantitative assessment of neurocognitive function across a range of cognitive domains
- The targeted sample size will permit statistically powered conclusions to be drawn from primary and secondary analyses
- The study protocol will be conducted at a single centre

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3 **INTRODUCTION**

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8 Due to advances in critical care, the number of individuals surviving critical illness has increased

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10 significantly over the past two decades. This increased survivorship has led to recognition of

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12 post-intensive care unit (ICU) syndrome, characterized by long-term cognitive, psychological,

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14 and functional limitations¹. For example, one year following ICU admission, survivors have

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16 cognitive performance similar to individuals with mild dementia or moderate traumatic brain

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18 injury². These impairments have important implications for quality of life, as only approximately

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20 two-thirds of previously employed individuals ever return to work following their ICU stay^{3 4}.

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22 The underlying cause of this cognitive impairment after critical illness is unclear, although it is

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24 known that delirium is one of the most consistent risk factors for long-term cognitive

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26 impairment⁵.

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33 Delirium is an acute change in level of consciousness, characterized by impaired attention and

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35 disorganized thinking, affecting up to 80% of critically ill patients⁶. Our group has demonstrated

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37 that low cerebral oxygenation, as measured by near-infrared spectroscopy (NIRS), is an

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39 independent risk factor for delirium in critically ill patients⁷. However, delirium is clearly

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41 multifactorial, and other key risk factors have also been described, including acute kidney injury

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43 (AKI)⁸.

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49 The incidence of severe AKI is on the rise, with up to 13% of adults admitted to ICUs per year

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51 requiring kidney replacement therapy (KRT⁹)¹⁰⁻¹². Outpatient KRT in the form of intermittent

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53 hemodialysis (iHD) and peritoneal dialysis (PD) has been linked to poor neurocognitive

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outcomes due to vascular and metabolic disturbances¹³, and adults initiated on dialysis in the ICU may be particularly at risk due to their superimposed critical illness.

The goal of this study is to examine the relationship between KRT, delirium, and long-term structural and cognitive outcomes in critically ill patients. We urgently need the results of such studies to reveal risk factors for poor cognitive and neurological outcomes in patients treated with KRT after ICU discharge, and to inform how different KRT modalities affect cognitive function in these vulnerable patients.

Overall Hypothesis

We hypothesize that KRT negatively impacts cerebral oxygenation, with downstream effects on delirium and long-term structural and functional neurological consequences at 3- and 12-months. We further hypothesize that iHD is a risk factor for lower cerebral oxygenation relative to CKRT, due to rapid hemodynamic shifts. These impairments will have negative effects on patient quality of life.

Kidney Replacement Therapy in the ICU

The decision to initiate KRT in patients admitted to the ICU is largely driven by medically refractory fluid overload, uremia, electrolyte disturbances, or metabolic acidosis, often in the setting of severe AKI (¹⁴). The burden of dialysis-requiring AKI is rising^{15 16}, particularly among critically ill adults¹⁵. Over half of all adults admitted to the ICU will develop AKI¹¹, with 3-13% ultimately requiring treatment with KRT¹². The risk of acquiring AKI among hospitalized or

critically ill patients further increases with age and the presence of other comorbid conditions including chronic kidney disease, heart disease, hypertension, diabetes, dementia, and cancer¹⁷.

Three modalities of KRT are available for use in the acute setting: iHD, continuous KRT (CKRT), and PD, with the former two being the most frequently used in patients admitted to the ICU¹⁸. iHD provides the most efficient clearance, but is poorly tolerated in hemodynamically unstable patients (e.g., those requiring hemodynamic support with vasopressors)¹⁹. CKRT uses slower rates of blood and dialysate flow over longer time periods, and is consequently more amenable to use in unstable populations²⁰. Many patients started on CKRT are often later transitioned to iHD as they become more capable of tolerating rapid hemodynamic shifts. However, unlike CKRT in which the brain’s ability to regulate blood flow in response to changing blood pressures (cerebral autoregulation) appears to be unperturbed²¹, the rapid shifts during iHD are known to affect cerebral perfusion²². No studies to date have explored the implications of dialysis or of transitioning from CKRT to iHD on cerebral perfusion.

rSO2 as a surrogate marker of cerebral perfusion during critical illness and kidney replacement therapy

Regional cerebral oxygen saturation (rSO2) in the frontal cortex—a surrogate marker of overall brain oxygenation—is a reliable marker of cerebral perfusion²³ and can be used to evaluate cerebral autoregulation²⁴. rSO2 can be measured in critically ill patients using near-infrared spectroscopy (NIRS), in which a light sensor placed on the patient’s forehead is used to non-invasively assess the oxygenation level of hemoglobin in the underlying brain tissue²⁵. Cerebral blood flow and rSO2 are reduced in adults with end-stage kidney disease (ESKD) undergoing

long-term maintenance dialysis²⁶, and have been associated with poor cognitive outcomes²⁷⁻²⁹. Moreover, low rSO₂ in other populations has been correlated with neurological abnormalities on brain imaging³⁰. Still, longitudinal studies examining the consequences of *short-term* acute dialysis on rSO₂ and its relationship with long-term cognitive function and neuroimaging have yet to be undertaken.

Rapid changes in mean arterial pressure (MAP) during iHD are generally well tolerated among stable individuals in the ICU, and providers have traditionally operated under the assumption that cerebral autoregulation is unperturbed by these rapid hemodynamic shifts. However, recent data from our group has demonstrated that cerebral autoregulation is disturbed in critically ill patients not undergoing dialysis³¹. An understanding of the consequences of dialysis on cerebral autoregulation in critically ill patients is needed to guide decision-making regarding choice of KRT modality in the ICU.

Neurocognitive outcomes of KRT

Maintenance dialysis is associated with short- and long-term neurocognitive impairment, including a decline in executive function³²⁻³⁵. Up to 70% of patients undergoing maintenance iHD demonstrate cognitive impairment³⁶. Studies in patients with chronic kidney disease (CKD) have posited that for every 10 mL/min/1.73m² decline in estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73m², an 11% increased prevalence of cognitive dysfunction occurs³⁷. This decline is further pronounced in individuals with CKD undergoing treatment with dialysis, due to their increased risk for cerebrovascular disease^{27 38}. Despite this understanding of the cognitive outcomes of kidney dysfunction and KRT in the chronic setting, the neurocognitive

impact of acute KRT remains largely unknown, and cognition has seldom been the focus of KRT trials in the ICU.

Patients on iHD may be particularly vulnerable to adverse neurocognitive effects, as a result of the rapid hemodynamic shifts that occur during treatment. To this end, cognitive fluctuations have been noted as a consequence of iHD, including deterioration in cognitive function post-iHD compared with pre-iHD levels, particularly in areas of attention and executive function³⁹.

Kidney disease and critical illness independently predict long-term structural brain pathology

Adults with CKD exhibit structural neurological changes on neuroimaging. eGFR has been inversely associated with white matter microstructural integrity in a diffusion tensor imaging (DTI) study of the brain, as evidenced by lower fractional anisotropy (FA) and higher mean diffusivity (MD) in healthy controls⁴⁰. Furthermore, CKD has been linked to global brain atrophy, demonstrated by increased lateral ventricle and sulci dilation⁴¹, and reduced white matter volume⁴².

Additional neuroimaging findings have been found in those with CKD on dialysis. White matter hyperintensities are more prevalent in patients on iHD relative to their healthy counterparts⁴³, and those on iHD have an increased ventricular-brain ratio relative to healthy controls⁴⁴.

ICU survivors show a similar increase in ventricle-brain ratio suggestive of cerebral atrophy compared to age-matched controls⁴⁵. In the same study, the authors found a correlation between

duration of delirium and degree of frontal and temporal lobe atrophy⁴⁵. It is not clear whether any patients in that study had CKD, AKI or required CKRT.

Study aims and hypotheses

1. Impact of dialysis on rSO₂ and delirium

Patients on maintenance dialysis experience an intradialytic reduction in cerebral oxygenation²³. Reduced cerebral oxygenation in other contexts in the ICU is known to be associated with delirium⁷. The effect of dialysis on rSO₂, and the effect of intradialytic rSO₂ on delirium in the ICU is unknown. We hypothesize that patients undergoing KRT will demonstrate an intradialytic drop in rSO₂ from baseline, and that more pronounced reductions in rSO₂ will be associated with increased severity of delirium.

2. Long-term consequences of intradialytic rSO₂ at 3- and 12-months post-ICU discharge

The long term impact of alterations in cerebral oxygenation during acute dialysis are unknown. We hypothesize that intradialytic rSO₂ during acute dialysis will be correlated with reduced neurocognitive function at 3- and 12-months after ICU discharge, and that patients with worse delirium scores will exhibit greater cognitive dysfunction. We further hypothesize that cognitive impairment at 3- and 12-months will be associated with an increased risk for poorer adherence to treatment regimens, adverse events, and increased rate of driving accidents⁴⁶.

Poor kidney function is associated with structural neurological impairment in patients with CKD and on maintenance dialysis. Low cerebral oxygenation and delirium are independently

correlated with neurological abnormalities on imaging. The effect of dialysis and rSO2 during critical illness on structural neuroanatomy is unknown. We hypothesize that severe, prolonged delirium and lower rSO2 during dialysis in the ICU are associated with structural neurological impairment at a macro- and micro-structural level.

3. Differential effects of different dialysis modalities on rSO2

Patients on maintenance dialysis exhibit lower rSO2 during dialysis sessions²³; the impact of short-term dialysis on rSO2 is unknown. We hypothesize that iHD is a risk factor for lower rSO2 vs. CKRT, due to rapid hemodynamic shifts.

Hypothesized causal pathway

The hypothesized causal pathway is outlined in *Figure 1*. AKI resulting in the receipt of KRT will lead to a reduction in cerebral oxygenation from baseline. This reduced cerebral oxygenation will be associated with an increased risk for delirium. Downstream consequences of low cerebral oxygenation and delirium will include reduced brain structural integrity (as evidenced by high mean diffusivity [MD] and low fractional anisotropy [FA]), increased brain atrophy, reduced cognitive function, and reduced patient well-being, (evidenced by a lower ability to adhere to prescribed medication regimens, and reduced driving safety).

METHODS AND ANALYSIS

Patient and public involvement

Patient representatives who have experienced critical illness will be sought prior to study initiation, to inform both patient-centered long-term outcome data collection as well as knowledge dissemination.

Study design and setting

This is a prospective, observational cohort study of critically ill participants initiated on acute KRT (iHD or CKRT). The INCOGNITO-AKI study will take place in a 33-bed medical-surgical intensive care unit at a tertiary academic hospital in Ontario, Canada.

Eligibility criteria

The inclusion criteria for the INCOGNITO-AKI study are: age greater than or equal to 18 years; admitted to the KHSC ICU; diagnosis of severe AKI requiring KRT (defined by the presence of either a twofold increase in serum creatinine from baseline, serum creatinine level greater than or equal to 354 $\mu\text{mol/L}$ with an increase of 27 $\mu\text{mol/L}$ from baseline, or urine output <6 mL/kg in the preceding 12 hours⁴⁷); and within 12 hours of initiation of KRT via iHD or CKRT.

Patients will be excluded from the study if they have acquired or congenital neurological disorders; any contraindication to testing with cerebral oximetry, Kinarm, or MRI (e.g., claustrophobia, limb amputation, paresis, neuromuscular disorders, etc.); KRT via PD; failure to consent; life expectancy less than 24 hours; clinical suspicion of renal obstruction, rapidly progressive glomerulonephritis or interstitial nephritis; or prehospitalization eGFR <30 mL/min/1.73m².

Recruitment and consent

Patients will be screened for eligibility and recruited by the research team from the KHSC ICU within 12 hours of initiation of KRT. Patients will be evaluated for capacity to consent on an ongoing basis. If unable to consent individually, consent will be obtained from the participant’s substitute decision maker.

Participants will be informed of their right to withdraw from the study at any time. Should a participant feel claustrophobic within the MRI or Kinarm robotic device during any of the assessments, or experience any other perceived or real adverse symptoms, the assessment will be stopped immediately, and the participant will be given the option of reattempting the assessment at a later date or withdrawing from the study altogether.

To facilitate recruitment and retention, compensation for time and travel will be provided. Follow-up visits will be scheduled when patients are already returning to KHSC for clinical care, and will be offered at flexible times. Recruitment materials will represent the diverse spectrum of age, sex, and gender within the critical care population.

Upon consent, participants will undergo a variety of assessments in accordance with the INCOGNITO-AKI Study Schema (*Figure 2*). Assessments will be obtained purely for investigational purposes and will not alter the patient’s treatment in any way.

Data collection

Patients admitted to the KHSC ICU receiving KRT will be enrolled within 12 hours of KRT initiation (ideally within 6 hours). Reasons for exclusion of screened but ineligible participants will be recorded. Baseline data including demographic information (age, sex, gender, ethnicity, geographic location [first 3 digits of postal code]), medications (including antihypertensive medications), comorbidities (including hypertension and history of mental illness e.g., depression, anxiety), reason for ICU admission, frailty (assessed by Clinical Frailty Scale, CFS), baseline cognition (Clinical Dementia Rating Scale, CDRS) and illness severity (assessed via Acute Physiological Assessment and Chronic Health Evaluation, APACHE II) will be collected from patient's medical records and via self-report.

Delirium will be assessed daily during ICU admission using the Confusion Assessment Method (CAM)-ICU-7 delirium severity scale⁴⁸. Additional ICU-specific data elements will be collected, including indication for dialysis, type of KRT (iHD vs. CKRT, if CKRT then CVVH vs. CVVHD vs. CVVHDF), indication for type of KRT, kidney function, dialysis-specific variables (dialysate/replacement fluid rates, electrolytes, access, blood flow, rate of fluid removal, hyper- and hypotensive episodes, duration of treatment, type of anticoagulation), duration of KRT, and ICU length-of-stay.

At time of hospital discharge, hospital length-of-stay, discharge destination, and kidney function (eGFR) will be recorded.

Outcomes

Cerebral oximetry

Cerebral oxygenation can be continuously monitored with non-invasive oximeters employing NIRS to generate rSO₂ values⁴⁹. Participants on CKRT will undergo continuous cerebral oximetry using the CASMED FORESIGHT Elite cerebral oximeter (Edwards LifeSciences, USA) during the first 72 hours of CKRT. Post-CKRT oximetry will be measured for 1 hour following completion of CKRT. Participants on iHD will undergo oximetry beginning 1 hour prior to each iHD session, continuously throughout each session, and ending 1 hour following completion of each session.

Neurocognitive testing

Kinarm

Kinarm End-Point Lab (Kinarm, Kingston, Canada), is an interactive robotic technology that uses a battery of behavioural tasks, called Kinarm Standard Tests (KST), that precisely quantifies sensory, motor, and neurocognitive impairment⁵⁰. Our group has previously demonstrated the feasibility of using the Kinarm for neurocognitive assessment in ICU survivors⁵¹. Participants will undergo serial Kinarm assessment at 3- and 12-months after discharge. Reasons for non-completion of Kinarm assessments will be recorded.

The specific Kinarm tasks to be used in the INCOGNITO-AKI study are outlined in *Table 1*.

Table 1. Kinarm tasks and domains of neurocognitive function assessed in the INCOGNITO-AKI study.

Task	Task type	Neurocognitive domain
Arm position matching	Sensorimotor	Somatosensory processing for perception, position-sense
Ball on bar	Sensorimotor	Bi-manual coordination, visuomotor skills
Visually guided reaching	Sensorimotor	Motor coordination, visuomotor skills, postural control of arm
Reverse visually guided reaching	Cognitive-motor	Visuomotor skills, cognitive ability to override automatic motor responses
Object hit	Cognitive-motor	Rapid visuomotor skills, bi-manual motor planning, spatial attention
Object hit and avoid	Cognitive-motor	Rapid motor decisions, bi-manual motor planning, spatial attention, executive function (attention and inhibitory control)
Trails A&B	Sensory-cognitive	Executive function, task switching
Paired Associate Learning	Sensory-cognitive	Visuospatial working memory

Adapted from the Kinarm user guide⁵².

All Kinarm task-specific parameters will be standardized to available normative control data generated as part of the validation process for the Kinarm robot, accounting for age, sex, handedness, and Kinarm platform effects⁵². Task-specific parameter values are then summed to generate global task scores for each participant, providing an assessment of overall performance on a given task. All scores will be normalized to *z*-scores. Neurocognitive impairment in the INCOGNITO-AKI study will be defined as a task *z*-score greater than the 95th percentile (i.e., *z*-scores greater than 1.64 indicate impairment on the given task relative to the healthy control cohort used to validate KST), in accordance with previously published literature using the Kinarm robot⁵³.

Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)

Global cognition will be assessed using the RBANS at the same time points. The RBANS is a 30-minute tool used to screen and quantify cognitive impairment in adults, across a variety of domains⁵⁴, and is commonly used to assess cognition in ICU survivors. Neurocognitive domains assessed through the RBANS include immediate and delayed memory, visuospatial/constructional, language, and attention⁵⁴.

Functional outcomes

Functional patient outcomes will be assessed at 12-months after discharge, and will include assessment of medication adherence using the Medication Adherence Rating Scale (MARS); assessment of adverse events including number of re-hospitalizations and emergency department visits; and driving safety (number of motor vehicle accidents, and Manchester Driver Behavior Questionnaire).

Structural neuroimaging

Patients will undergo serial structural magnetic resonance imaging (MRI) of the brain at 3- and 12-months after discharge. Anonymized and de-identified MRI scans will be processed using MIPAV⁵⁵ v.7.3.0 and Oxford Centre for Functional MRI of the Brain (FMRIB) Software Library (FSL)⁵⁶ v.5.0 medical image processing programs. Scans will be corrected for intensity non-uniformity⁵⁷ and transformed into a common image space to adjust for variations in head size and orientation⁵⁸. Skull stripping will be performed⁵⁹. Automated and semi-automated techniques will be used to determine whole-brain volumes from T1-weighted images^{59 60} for analysis of macrostructural brain integrity, as well as FA and MD measures from diffusion-weighted

images⁵⁸ for analysis of microstructural brain integrity. Brain volumes will be corrected for total intracranial volume to account for head size⁶¹. Reasons for non-completion of MRI scanning will be recorded. Patients will be used as their own controls over time using a within-subjects design.

Sample size

The relationship between cerebral oxygenation during dialysis and delirium in critically ill patients has not been previously explored. We have based our sample size on estimated enrolment rates. Approximately five new adult patients are initiated on KRT in the ICU per month at KHSC. Assuming a 90% consent rate based on our prior work, 54 patients per year will be enrolled in the INCOGNITO-AKI study over a two year period, yielding an estimated sample size of 108 patients. 108 subjects will provide 90% power to detect a correlation of 0.3 between two variables, and 90% power to detect a predictor that explains 9% of the remaining variance in a dependent variable of a linear regression model after controlling for other predictors in the model.

Data management

All information collected from patients will be recorded directly into a Research Electronic Data Capture (REDCap) database housed on the Queen's University server, which can only be accessed by study team members (<https://fhs.cac.queensu.ca/CNS/>). All patient identifiers will be coded and anonymized. All results from Kinarm and NIRS assessments will be assigned a numeric code associated with each subject and otherwise stripped of all identifying information, and with access restricted to study personnel only. A master linking log connecting patient's identifiable information (i.e., medical record number) to their study ID will be securely

maintained internally behind two locks, with access restricted to study personnel. MRI scans consisting of a series of DICOM (Digital Image Communication) files will be assigned a numeric code associated with each subject and otherwise stripped of all identifying information using a standard DICOM file anonymizer.

Statistical methods

Primary objectives

The primary objective of this study is the impact of intradialytic rSO2 on delirium during ICU admission, as measured by NIRS. Continuous rSO2 data throughout each form of dialysis will be summarized using three variables, which together comprise the cerebral perfusion index (CPI): 1) mean rSO2 throughout dialysis, 2) duration of disturbed cerebral autoregulation, and 3) the area under the curve (AUC) outside of the optimal mean arterial pressure (MAP)⁶². These three summary variables have been used to describe cerebral oxygenation in previous reports^{62 63}.

Mean rSO2 will be calculated for the duration of oximetry recording during the first CKRT session (1 hour pre-initiation, 72 hours during CKRT, and 1 hour post-cessation, as described above), and for each iHD session recording period (1 hour pre-initiation, throughout iHD, and for 1 hour post-cessation).

Cerebral autoregulation will be evaluated using the cerebral oximetry index (COx), with time-varying Spearman correlation coefficients calculated between rSO2 values and MAP at one-minute intervals throughout the duration of the oximetry recordings³¹. Positive values of the COx

($p < 0.0001$) are indicative of disturbed cerebral autoregulation³¹. Duration of disturbed cerebral autoregulation will be taken as the length of time during each recording session for which COx values were positive^{62 63}.

Optimal MAP \pm standard deviation (SD) will be calculated as the mean MAP for COx of 0 ± 1 SD⁶². AUC outside of the optimal MAP will be taken as the proportion of the AUC where AUC was outside of the range of the optimal MAP⁶².

Multiple linear regression using CPI parameters as the independent predictor variables and cumulative CAM-ICU-7 score throughout the patient's ICU stay as the response variable will be performed. The model will be built from the following potential covariates: illness severity APACHE score, baseline cognition via CDRS, and baseline frailty via CFS.

Secondary objectives

To assess the relationship between rSO₂, delirium, and long-term cognitive impairment, multiple linear regression will be used to determine association between intradialytic rSO₂ (predictor variables) and neurocognitive impairment via RBANS/Kinarm scores at 3- and 12-months (response variables), controlling for covariates (frailty, dementia, illness severity, delirium).

Association between rSO₂ values (predictor) and each of brain volume, FA and MD (outcomes) will be assessed through multiple linear regression. Baseline CDRS score, APACHE score, and CFS will be included as covariates. Linear regression will be used to determine association between structural brain pathology (total brain volume, FA, and MD) and neurocognitive

function (RBANS/Kinarm scores), as well as patient well-being (adverse events, MARS, and MDBQ scores) at 3- and 12-months post-discharge.

Tertiary/exploratory objectives

Our exploratory objective is to assess the differential effect of iHD and CKRT on cerebral oxygenation. To this end, analysis of covariance (ANCOVA) will be used to assess effect of first dialysis modality (iHD vs. CKRT) on integrated intradialytic rSO2 values, while controlling for covariates. Integrated rSO2 values will be used to determine differential changes from baseline throughout iHD and CKRT.

ETHICS AND DISSEMINATION

This study has been approved by the Queen’s University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board (HSREB), REB approval number: DMED-2424-20. The study protocol does not interfere in any way with the standard of care provided to patients.

Risks of participation

Use of the Kinarm and NIRS are low-risk. There is a risk of incidental findings discovered by Kinarm. In this event, participants will be referred to a neurologist for further examination. Results will be communicated to the participant and/or family via a brief written research report. There is a risk of skin irritation due to the adhesive used in the NIRS device.

MRI is low-risk. No contrast agents (e.g., gadolinium) will be used due to the risk of

nephrogenic systemic fibrosis (NSF) in patients with kidney impairment. There is a risk of incidental findings discovered by MRI. In this event, participants will be referred to a neurologist for further examination. Results will be communicated to the participant and/or family via a brief written research report.

In spite of our best efforts, if personal health information is inappropriately released, we will take measures to ensure that further release of information is stopped, that any information which can be retrieved is retrieved immediately, and that the KHSC and Queen's University Privacy Office and REB will be notified. Further actions may be taken according to recommendations from the Privacy Office and REB.

Knowledge translation

Prior to study initiation, functional patient-centered outcomes will be sought from diverse patient representatives who have experienced critical illness, and included in the follow-up data collection for the INCOGNITO-AKI study to elucidate meaningful consequences of poor cognition. To inform knowledge translation, these representatives will also be asked for input on how to disseminate and increase accessibility of study results (e.g., multiple languages, print and electronic dissemination, use of text and graphics to represent data, etc.). Results of the INCOGNITO-AKI study will be presented at critical care conferences, and disseminated to ICU patients and families in their preferred method.

Significance

Initiation of acute KRT is increasingly common in critically ill adults admitted to the ICU. This project will provide crucial insight into the early neurological changes occurring in these patients, and their short- and long-term impact on cognitive function. If we discover that cerebral oxygenation is lower when patients are on iHD vs. when they are on CKRT and that this reduction is associated with poorer cognition and neuroimaging findings, this will provide a rationale for developing a protocol to maximize rSO₂ and control ultrafiltration rate during iHD. This understanding will further serve as a foundation for developing interventions to improve neurological outcomes in this vulnerable cohort, thereby reducing their overall morbidity and mortality and relieving stress on an already burdened healthcare system.

AUTHOR CONTRIBUTIONS

JG Boyd and NA Jawa designed the study and wrote the study protocol. NA Jawa drafted and revised the manuscript. JG Boyd, RM Holden, SA Silver, BYM Kwan, PA Norman, AG Day, J Muscedere, and SH Scott reviewed and revised the manuscript. SH Scott developed, designed and manages the Kinarm robotic labs that will be used in the INCOGNITO-AKI study.

FUNDING STATEMENT

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

COMPETING INTERESTS STATEMENT

SH Scott is co-founder and CSO of Kinarm that commercializes the Kinarm robotic technology used in the present study. NA Jawa, RM Holden, SA Silver, AG Day, PA Norman, BYM Kwan, DM Maslove, J Muscedere, and JG Boyd have no conflicts of interest to declare.

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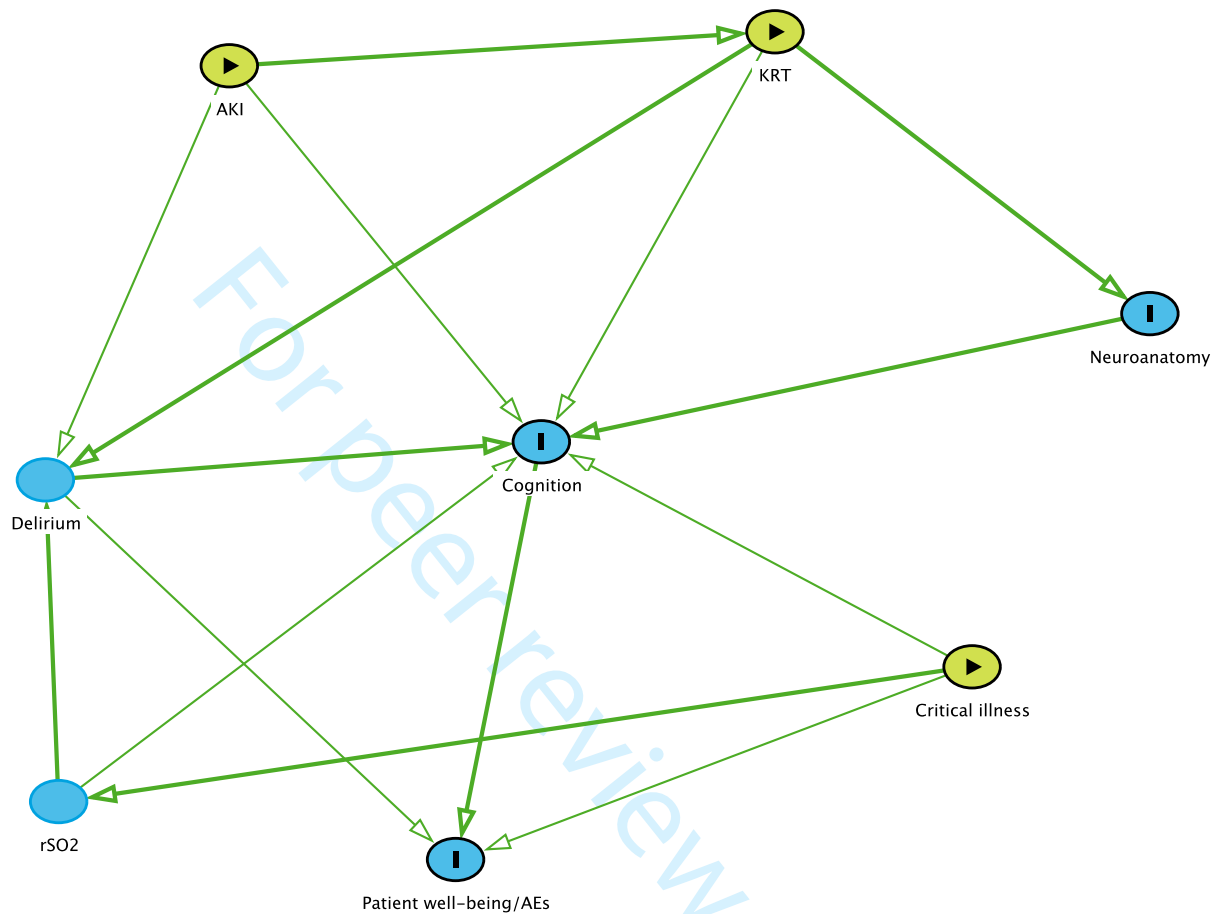
FIGURE LEGENDS

Figure 1. Hypothesized causal pathway.

Figure 2. Study schema.

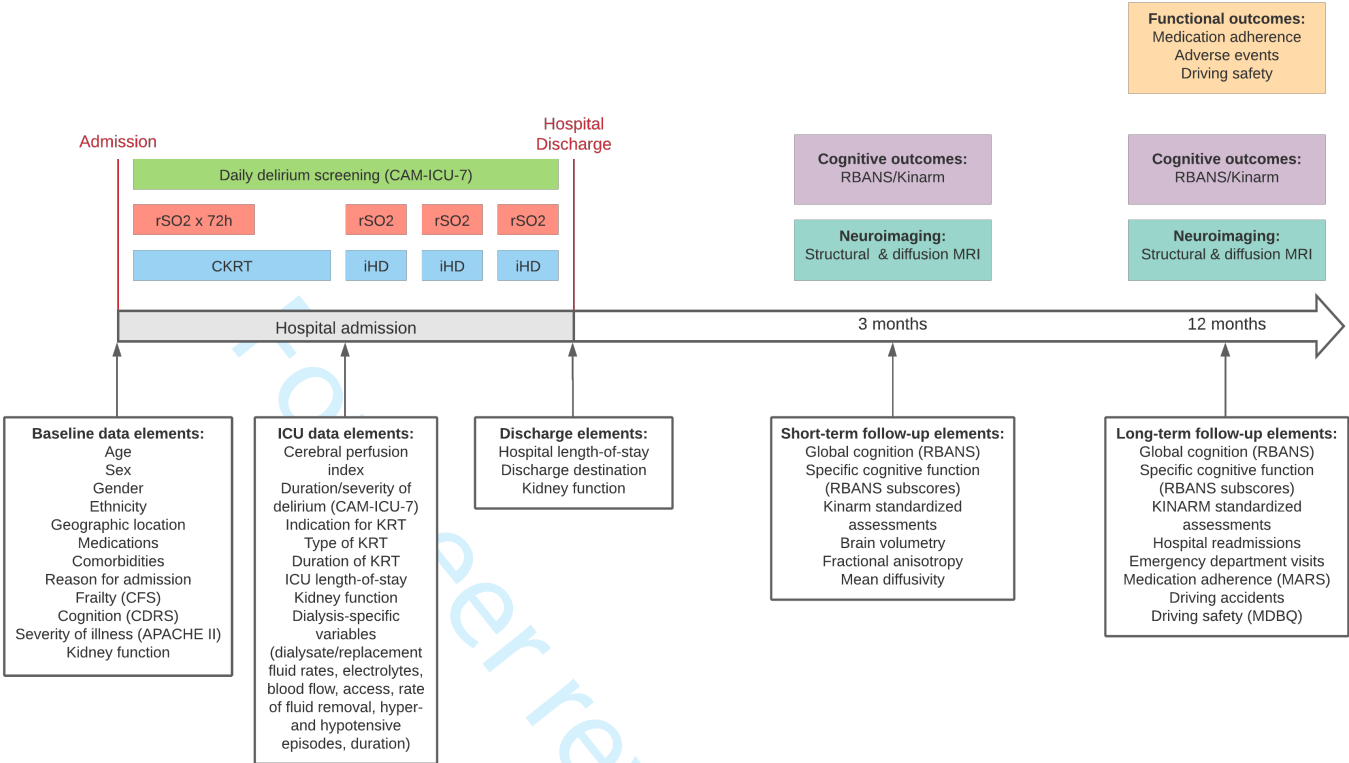
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Figure 1. Hypothesized causal pathway.



Green arrows represent causal paths; blue circles represent ancestors of outcome variables; blue circles with a line represent outcome variables; green circles with a triangle represent exposures. Cerebral oxygenation (rSO₂); acute kidney injury (AKI); kidney replacement therapy (KRT); adverse events (AEs).

Figure 2. Study schema.



Cerebral oxygenation (rSO₂); kidney replacement therapy (KRT); continuous KRT (CKRT); intermittent hemodialysis (iHD); Clinical Frailty Scale (CFS); Clinical Dementia Rating Scale (CDRS); Acute Physiological Assessment and Chronic Health Evaluation (APACHE II); Confusion Assessment Method-ICU-7 (CAM-ICU-7); Repeatable Battery for the Assessment of Neuropsychological Status (RBANS); Medication Adherence Rating Scale (MARS); Manchester Driver Behaviour Questionnaire (MDBQ).

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

			Page Number
Reporting Item			
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	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	24
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 24

1	Roles and	#5b	Name and contact information for the trial sponsor	N/A
2	responsibilities:			
3	sponsor contact			
4	information			
5				
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8	Roles and	#5c	Role of study sponsor and funders, if any, in study design;	N/A
9	responsibilities:		collection, management, analysis, and interpretation of data;	
10	sponsor and funder		writing of the report; and the decision to submit the report for	
11			publication, including whether they will have ultimate	
12			authority over any of these activities	
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16	Roles and	#5d	Composition, roles, and responsibilities of the coordinating	N/A
17	responsibilities:		centre, steering committee, endpoint adjudication committee,	
18	committees		data management team, and other individuals or groups	
19			overseeing the trial, if applicable (see Item 21a for data	
20			monitoring committee)	
21				
22				
23				
24	Introduction			
25				
26				
27	Background and	#6a	Description of research question and justification for	6-11
28	rationale		undertaking the trial, including summary of relevant studies	
29			(published and unpublished) examining benefits and harms for	
30			each intervention	
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34	Background and	#6b	Explanation for choice of comparators	N/A
35	rationale: choice of			
36	comparators			
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39	Objectives	#7	Specific objectives or hypotheses	11-12
40				
41	Trial design	#8	Description of trial design including type of trial (eg, parallel	
42			group, crossover, factorial, single group), allocation ratio, and	
43			framework (eg, superiority, equivalence, non-inferiority,	
44			exploratory)	
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48	Methods:			
49	Participants,			
50	interventions, and			
51	outcomes			
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55	Study setting	#9	Description of study settings (eg, community clinic, academic	12-13
56			hospital) and list of countries where data will be collected.	
57			Reference to where list of study sites can be obtained	
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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)	13
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	14-18
Interventions: modifications	#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)	14
Interventions: adherence	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	14
Interventions: concomitant care	#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	15-18
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)	13-18; Figure 2
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	18
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	13, 18

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; not a controlled trial
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; not a controlled trial
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A; not a controlled trial
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A; not a controlled trial
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A; not a controlled trial
Methods: Data collection, management, and analysis			
Data collection plan	#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	14-15
Data collection plan: retention	#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	16, 18

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	18-19
Statistics: outcomes	#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	19-21
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	21
Statistics: analysis population and missing data	#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)	N/A
Methods: Monitoring			
Data monitoring: formal committee	#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
Data monitoring: interim analysis	#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	N/A
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	21

1	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
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8	Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	13-14
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13	Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
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18	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	18-19
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24	Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	24
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28	Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18-19
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33	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
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37	Dissemination policy: trial results	#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	22
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45	Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
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49	Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
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53	Appendices			
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55	Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
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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

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BMJ Open

Identifying neurocognitive outcomes and cerebral oxygenation in critically ill adults on acute kidney replacement therapy in the intensive care unit: The INCOGNITO-AKI study protocol

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Title: Identifying neurocognitive outcomes and cerebral oxygenation in critically ill adults on acute kidney replacement therapy in the intensive care unit: The INCOGNITO-AKI study protocol

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ABSTRACT

Introduction. Initiation of acute kidney replacement therapy (KRT) is common in critically ill adults admitted to the intensive care unit (ICU), and associated with increased morbidity and mortality. KRT has been linked to poor neurocognitive outcomes, leading to reduced quality of life, and increased utilization of healthcare resources. Adults on dialysis in the ICU may be particularly at risk of neurocognitive impairment, as survivors of critical illness are already predisposed to developing cerebrovascular disease and cognitive dysfunction long-term relative to healthy controls. Regional cerebral oxygen saturation (rSO2) may provide a critical early marker of long-term neurocognitive impairment in this population. This study aims to understand cerebral oxygenation in patients undergoing KRT (continuous or intermittent) in the ICU. These findings will be correlated with long-term cognitive and functional outcomes, and structural brain pathology.

Methods and analysis. 108 patients scheduled to undergo treatment for acute kidney injury with KRT in the Kingston Health Sciences Centre ICU will be recruited into this prospective

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4 observational study. Enrolled patients will be assessed with intradialytic cerebral oximetry using
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7 near infrared spectroscopy (NIRS). Delirium will be assessed daily with the Confusion
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10 Assessment Method-Intensive Care Unit (CAM-ICU) and severity quantified as cumulative
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13 CAM-ICU-7 scores. Neurocognitive impairment will be assessed at 3- and 12-months after
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16 hospital discharge using the Kinarm and Repeatable Battery for the Assessment of
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19 Neuropsychological Status (RBANS). Structural brain pathology on MRI will also be measured
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22 at the same timepoints. Driving safety, adverse events, and medication adherence will be
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25 assessed at 12-months to evaluate the impact of neurocognitive impairment on functional
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28 outcomes.
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37 **Ethics and dissemination.** This study is approved by the Queen's University Health
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40 Sciences/Affiliated Teaching Hospitals Research Ethics Board (DMED-2424-20). Results will be
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43 presented at critical care conferences, and a lay summary will be provided to patients in their
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54 **Trial registration number.** NCT04722939.
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ARTICLE SUMMARY

Strengths and limitations of this study:

- This will be the first study to use a comprehensive battery of neurological tests to interrogate both short- and long-term neurological impairment in critically ill adults on dialysis
- This study will employ robotic technology in a novel patient population to provide a quantitative assessment of neurocognitive function across a range of cognitive domains
- The targeted sample size will permit statistically powered conclusions to be drawn from primary and secondary analyses
- The study protocol will be conducted at a single centre

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INTRODUCTION

Due to advances in critical care, the number of individuals surviving critical illness has increased significantly over the past two decades. This increased survivorship has led to recognition of post-intensive care unit (ICU) syndrome, characterized by long-term cognitive, psychological, and functional limitations¹. For example, one year following ICU admission, survivors have cognitive performance similar to individuals with mild dementia or moderate traumatic brain injury². These impairments have important implications for quality of life, as only approximately two-thirds of previously employed individuals ever return to work following their ICU stay^{3 4}. The underlying cause of this cognitive impairment after critical illness is unclear, although it is known that delirium is one of the most consistent risk factors for long-term cognitive impairment⁵.

Delirium is an acute change in level of consciousness, characterized by impaired attention and disorganized thinking, affecting up to 80% of critically ill patients⁶. Our group has demonstrated that low cerebral oxygenation, as measured by near-infrared spectroscopy (NIRS), is an

independent risk factor for delirium in critically ill patients⁷. However, delirium is clearly multifactorial, and other key risk factors have also been described, including acute kidney injury (AKI)⁸.

The incidence of severe AKI is on the rise, with up to 13% of adults admitted to ICUs per year requiring kidney replacement therapy (KRT⁹)¹⁰⁻¹². Outpatient KRT in the form of intermittent hemodialysis (iHD) and peritoneal dialysis (PD) has been linked to poor neurocognitive outcomes due to vascular and metabolic disturbances¹³, and adults initiated on dialysis in the ICU may be particularly at risk due to their superimposed critical illness.

The goal of this study is to examine the relationship between KRT, delirium, and long-term structural and cognitive outcomes in critically ill patients. We urgently need the results of such studies to reveal risk factors for poor cognitive and neurological outcomes in patients treated with KRT after ICU discharge, and to inform how different KRT modalities affect cognitive function in these vulnerable patients.

Overall Hypothesis

We hypothesize that KRT is associated with low cerebral oxygenation, which in turn will be associated with delirium and long-term structural and functional neurological consequences at 3- and 12-months. We further hypothesize that iHD is a risk factor for lower cerebral oxygenation relative to CKRT, due to rapid hemodynamic shifts. These impairments will have negative effects on patient quality of life.

Kidney Replacement Therapy in the ICU

The decision to initiate KRT in patients admitted to the ICU is largely driven by medically refractory fluid overload, uremia, electrolyte disturbances, or metabolic acidosis, often in the setting of severe AKI (¹⁴). The burden of dialysis-requiring AKI is rising^{15 16}, particularly among critically ill adults¹⁵. Over half of all adults admitted to the ICU will develop AKI¹¹, with 3-13% ultimately requiring treatment with KRT¹². The risk of acquiring AKI among hospitalized or critically ill patients further increases with age and the presence of other comorbid conditions including chronic kidney disease, heart disease, hypertension, diabetes, dementia, and cancer¹⁷.

Three modalities of KRT are available for use in the acute setting: iHD, continuous KRT (CKRT), and PD, with the former two being the most frequently used in patients admitted to the ICU¹⁸. iHD provides the most efficient clearance, but is poorly tolerated in hemodynamically unstable patients (e.g., those requiring hemodynamic support with vasopressors)¹⁹. CKRT uses slower rates of blood and dialysate flow over longer time periods, and is consequently more amenable to use in unstable populations²⁰. Many patients started on CKRT are often later transitioned to iHD as they become more capable of tolerating rapid hemodynamic shifts. However, unlike CKRT in which the brain's ability to regulate blood flow in response to changing blood pressures (cerebral autoregulation) appears to be unperturbed²¹, the rapid shifts during iHD are known to affect cerebral perfusion²². No studies to date have explored the implications of dialysis or of transitioning from CKRT to iHD on cerebral perfusion.

rSO₂ as a surrogate marker of cerebral perfusion during critical illness and kidney replacement therapy

Regional cerebral oxygen saturation (rSO₂) in the frontal cortex—a surrogate marker of overall brain oxygenation—is a reliable marker of cerebral perfusion²³ and can be used to evaluate

cerebral autoregulation²⁴. rSO₂ can be measured in critically ill patients using near-infrared spectroscopy (NIRS), in which a light sensor placed on the patient's forehead is used to non-invasively assess the oxygenation level of hemoglobin in the underlying brain tissue²⁵. Cerebral blood flow and rSO₂ are reduced in adults with end-stage kidney disease (ESKD) undergoing *long-term* maintenance dialysis²⁶, and have been associated with poor cognitive outcomes²⁷⁻²⁹. Moreover, low rSO₂ in other populations has been correlated with neurological abnormalities on brain imaging³⁰. Still, longitudinal studies examining the consequences of *short-term* acute dialysis on rSO₂ and its relationship with long-term cognitive function and neuroimaging have yet to be undertaken.

Rapid changes in mean arterial pressure (MAP) during iHD are generally well tolerated among stable individuals in the ICU, and providers have traditionally operated under the assumption that cerebral autoregulation is unperturbed by these rapid hemodynamic shifts. However, recent data from our group has demonstrated that cerebral autoregulation is disturbed in critically ill patients not undergoing dialysis³¹. An understanding of the consequences of dialysis on cerebral

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4 autoregulation in critically ill patients is needed to guide decision-making regarding choice of
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7 KRT modality in the ICU.
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13 **Neurocognitive outcomes of AKI**

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17 AKI is associated with an increased risk for long-term neurological issues, including
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20 inflammation, stroke, delirium, and cognitive deficits, including dementia³²⁻³⁵. Prior research by
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23 our group has further demonstrated that survivors of AKI experience quantifiable deficits in the
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26 areas of attention, visuomotor, and executive function³⁶.
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33 **Neurocognitive outcomes of KRT**

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37 Maintenance dialysis is associated with short- and long-term neurocognitive impairment,
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40 including a decline in executive function³⁷⁻⁴⁰. Up to 70% of patients undergoing maintenance
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43 iHD demonstrate cognitive impairment⁴¹. Studies in patients with chronic kidney disease (CKD)
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46 have posited that for every 10 mL/min/1.73m² decline in estimated glomerular filtration rate
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49 (eGFR) below 60 mL/min/1.73m², an 11% increased prevalence of cognitive dysfunction
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52 occurs⁴². This decline is further pronounced in individuals with CKD undergoing treatment with
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dialysis, due to their increased risk for cerebrovascular disease^{27 43}. Despite this understanding of the cognitive outcomes of kidney dysfunction and KRT in the chronic setting, the neurocognitive impact of acute KRT remains largely unknown, and cognition has seldom been the focus of KRT trials in the ICU.

Patients on iHD may be particularly vulnerable to adverse neurocognitive effects, as a result of the rapid hemodynamic shifts that occur during treatment. To this end, cognitive fluctuations have been noted as a consequence of iHD, including deterioration in cognitive function post-iHD compared with pre-iHD levels, particularly in areas of attention and executive function⁴⁴.

Kidney disease and critical illness independently predict long-term structural brain pathology

Adults with CKD exhibit structural neurological changes on neuroimaging. eGFR has been inversely associated with white matter microstructural integrity in a diffusion tensor imaging (DTI) study of the brain, as evidenced by lower fractional anisotropy (FA) and higher mean diffusivity (MD) in healthy controls⁴⁵. Furthermore, CKD has been linked to global brain

atrophy, demonstrated by increased lateral ventricle and sulci dilation⁴⁶, and reduced white matter volume⁴⁷.

Additional neuroimaging findings have been found in those with CKD on dialysis. White matter hyperintensities are more prevalent in patients on iHD relative to their healthy counterparts⁴⁸, and those on iHD have an increased ventricular-brain ratio relative to healthy controls⁴⁹.

ICU survivors show a similar increase in ventricle-brain ratio suggestive of cerebral atrophy compared to age-matched controls⁵⁰. In the same study, the authors found a correlation between duration of delirium and degree of frontal and temporal lobe atrophy⁵⁰. It is not clear whether any patients in that study had CKD, AKI or required CKRT.

Study aims and hypotheses

1. Impact of dialysis on rSO₂ and delirium

Patients on maintenance dialysis experience an intradialytic reduction in cerebral oxygenation²³.

Reduced cerebral oxygenation in other contexts in the ICU is known to be associated with

delirium⁷. The effect of dialysis on rSO₂, and the effect of intradialytic rSO₂ on delirium in the

ICU is unknown. We hypothesize that patients undergoing KRT will demonstrate an intradialytic

drop in rSO₂ from baseline, and that more pronounced reductions in rSO₂ will be associated

with increased severity of delirium.

2. Long-term consequences of intradialytic rSO₂ at 3- and 12-months post-ICU discharge

The long term impact of alterations in cerebral oxygenation during acute dialysis are unknown.

We hypothesize that intradialytic rSO₂ during acute dialysis will be correlated with reduced

neurocognitive function at 3- and 12-months after ICU discharge, and that patients with worse

delirium scores will exhibit greater cognitive dysfunction. We further hypothesize that cognitive

impairment at 3- and 12-months will be associated with an increased risk for poorer adherence to

treatment regimens, adverse events, and increased rate of driving accidents⁵¹.

Poor kidney function is associated with structural neurological impairment in patients with CKD and on maintenance dialysis. Low cerebral oxygenation and delirium are independently correlated with neurological abnormalities on imaging. The effect of dialysis and rSO₂ during critical illness on structural neuroanatomy is unknown. We hypothesize that severe, prolonged delirium and lower rSO₂ during dialysis in the ICU are associated with structural neurological impairment at a macro- and micro-structural level.

3. Differential effects of different dialysis modalities on rSO₂

Patients on maintenance dialysis exhibit lower rSO₂ during dialysis sessions²³; the impact of short-term dialysis on rSO₂ is unknown. We hypothesize that iHD is a risk factor for lower rSO₂ vs. CKRT, due to rapid hemodynamic shifts.

Hypothesized causal pathway

The hypothesized causal pathway is outlined in *Figure 1*. AKI resulting in the receipt of KRT will lead to a reduction in cerebral oxygenation from baseline. This reduced cerebral oxygenation will be associated with an increased risk for delirium. Downstream consequences of low cerebral

oxygenation and delirium will include reduced brain structural integrity (as evidenced by high mean diffusivity [MD] and low fractional anisotropy [FA]), increased brain atrophy, reduced cognitive function, and reduced patient well-being, (evidenced by a lower ability to adhere to prescribed medication regimens, and reduced driving safety).

METHODS AND ANALYSIS

Patient and public involvement

Patient representatives who have experienced critical illness will be sought prior to study initiation, to inform both patient-centered long-term outcome data collection as well as knowledge dissemination.

Study design and setting

This is a prospective, observational cohort study of critically ill participants initiated on acute KRT (iHD or CKRT). The INCOGNITO-AKI study will take place in a 33-bed medical-surgical intensive care unit at a tertiary academic hospital in Ontario, Canada.

Eligibility criteria

The inclusion criteria for the INCOGNITO-AKI study are: age greater than or equal to 18 years; admitted to the KHSC ICU; diagnosis of severe AKI requiring KRT (defined by the presence of either a twofold increase in serum creatinine from baseline, serum creatinine level greater than or equal to 354 $\mu\text{mol/L}$ with an increase of 27 $\mu\text{mol/L}$ from baseline, or urine output $<6 \text{ mL/kg}$ in the preceding 12 hours⁵²); and within 12 hours of initiation of KRT via iHD or CKRT.

Patients will be excluded from the study if they have acquired or congenital neurological disorders; any contraindication to testing with cerebral oximetry, Kinarm, or MRI (e.g., claustrophobia, limb amputation, paresis, neuromuscular disorders, etc.); KRT via PD; failure to consent; life expectancy less than 24 hours; clinical suspicion of renal obstruction, rapidly progressive glomerulonephritis or interstitial nephritis; or prehospitalization eGFR $<30 \text{ mL/min/1.73m}^2$.

Recruitment and consent

Patients will be screened for eligibility and recruited by the research team from the KHSC ICU within 12 hours of initiation of KRT. Patients will be evaluated for capacity to consent on an ongoing basis. If unable to consent individually, consent will be obtained from the participant's substitute decision maker.

Participants will be informed of their right to withdraw from the study at any time. Should a participant feel claustrophobic within the MRI or Kinarm robotic device during any of the assessments, or experience any other perceived or real adverse symptoms, the assessment will be stopped immediately, and the participant will be given the option of reattempting the assessment at a later date or withdrawing from the study altogether.

To facilitate recruitment and retention, compensation for time and travel will be provided.

Follow-up visits will be scheduled when patients are already returning to KHSC for clinical care, and will be offered at flexible times. Recruitment materials will represent the diverse spectrum of age, sex, and gender within the critical care population.

Upon consent, participants will undergo a variety of assessments in accordance with the INCOGNITO-AKI Study Schema (*Figure 2*). Assessments will be obtained purely for investigational purposes and will not alter the patient's treatment in any way.

Data collection

Patients admitted to the KHSC ICU receiving KRT will be enrolled within 12 hours of KRT initiation (ideally within 6 hours). Reasons for exclusion of screened but ineligible participants will be recorded. Baseline data including demographic information (age, sex, gender, ethnicity, geographic location [first 3 digits of postal code]), medications (including antihypertensive medications), comorbidities (including hypertension and history of mental illness e.g., depression, anxiety), reason for ICU admission, frailty (assessed by Clinical Frailty Scale, CFS), baseline cognition (Clinical Dementia Rating Scale, CDRS) and illness severity (assessed via Acute Physiological Assessment and Chronic Health Evaluation, APACHE II) will be collected from patient's medical records and via self-report.

Delirium will be assessed daily during ICU admission using the Confusion Assessment Method (CAM)-ICU-7 delirium severity scale⁵³, which requires daily assessment using the Richmond Agitation Sedation Scale (RASS) to quantify patients' level of sedation/consciousness.

Additional ICU-specific data elements will be collected, including indication for dialysis, type of KRT (iHD vs. CKRT, if CKRT then CVVH vs. CVVHD vs. CVVHDF), indication for type of KRT, kidney function, dialysis-specific variables (dialysate/replacement fluid rates, electrolytes, access, blood flow, rate of fluid removal, hyper- and hypotensive episodes, duration of treatment, type of anticoagulation), duration of KRT, and ICU length-of-stay.

At time of hospital discharge, hospital length-of-stay, discharge destination, kidney function (eGFR), and ongoing maintenance dialysis requirements will be recorded.

During participants' 3- and 12-month follow-up visits, information on their maintenance dialysis requirements, as well as their most recent laboratory data for creatinine/eGFR, will be recorded.

Outcomes

Cerebral oximetry

Cerebral oxygenation can be continuously monitored with non-invasive oximeters employing NIRS to generate rSO₂ values⁵⁴. Participants on CKRT will undergo continuous cerebral oximetry using the CASMED FORESIGHT Elite cerebral oximeter (Edwards LifeSciences, USA) during the first 72 hours of CKRT. Post-CKRT oximetry will be measured for 1 hour following completion of CKRT. Participants on iHD will undergo oximetry beginning 1 hour prior to each iHD session, continuously throughout each session, and ending 1 hour following completion of each session.

Neurocognitive testing

Kinarm

Kinarm End-Point Lab (Kinarm, Kingston, Canada), is an interactive robotic technology that uses a battery of behavioural tasks, called Kinarm Standard Tests (KST), that precisely quantifies sensory, motor, and neurocognitive impairment⁵⁵. Our group has previously demonstrated the feasibility of using the Kinarm for neurocognitive assessment in ICU survivors⁵⁶. Participants

will undergo serial Kinarm assessment at 3- and 12-months after discharge. Reasons for non-completion of Kinarm assessments will be recorded.

The specific Kinarm tasks to be used in the INCOGNITO-AKI study are outlined in *Table 1*.

Table 1. Kinarm tasks and domains of neurocognitive function assessed in the INCOGNITO-AKI study.

Task	Task type	Neurocognitive domain
Arm position matching	Sensorimotor	Somatosensory processing for perception, position-sense
Ball on bar	Sensorimotor	Bi-manual coordination, visuomotor skills
Visually guided reaching	Sensorimotor	Motor coordination, visuomotor skills, postural control of arm
Reverse visually guided reaching	Cognitive-motor	Visuomotor skills, cognitive ability to override automatic motor responses
Object hit	Cognitive-motor	Rapid visuomotor skills, bi-manual motor planning, spatial attention
Object hit and avoid	Cognitive-motor	Rapid motor decisions, bi-manual motor planning, spatial

		attention, executive function (attention and inhibitory control)
Trails A&B	Sensory-cognitive	Executive function, task switching
Paired Associate Learning	Sensory-cognitive	Visuospatial working memory

Adapted from the Kinarm user guide⁵⁷.

All Kinarm task-specific parameters will be standardized to available normative control data generated as part of the validation process for the Kinarm robot, accounting for age, sex, handedness, and Kinarm platform effects⁵⁷. Task-specific parameter values are then summed to generate global task scores for each participant, providing an assessment of overall performance on a given task. All scores will be normalized to *z*-scores. Neurocognitive impairment in the INCOGNITO-AKI study will be defined as a task *z*-score greater than the 95th percentile (i.e., *z*-scores greater than 1.64 indicate impairment on the given task relative to the healthy control cohort used to validate KST), in accordance with previously published literature using the Kinarm robot⁵⁸.

Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)

Global cognition will be assessed using the RBANS at the same time points. The RBANS is a 30-minute tool used to screen and quantify cognitive impairment in adults, across a variety of domains⁵⁹, and is commonly used to assess cognition in ICU survivors. Neurocognitive domains assessed through the RBANS include immediate and delayed memory, visuospatial/constructional, language, and attention⁵⁹.

Functional outcomes

Functional patient outcomes will be assessed at 12-months after discharge, and will include assessment of medication adherence using the Medication Adherence Rating Scale (MARS); assessment of adverse events including number of re-hospitalizations and emergency department visits; and driving safety (number of motor vehicle accidents, and Manchester Driver Behavior Questionnaire).

Structural neuroimaging

Patients will undergo serial structural magnetic resonance imaging (MRI) of the brain at 3- and 12-months after discharge. Anonymized and de-identified MRI scans will be processed using

MIPAV⁶⁰ v.7.3.0 and Oxford Centre for Functional MRI of the Brain (FMRIB) Software Library (FSL)⁶¹ v.5.0 medical image processing programs. Scans will be corrected for intensity non-uniformity⁶² and transformed into a common image space to adjust for variations in head size and orientation⁶³. Skull stripping will be performed⁶⁴. Automated and semi-automated techniques will be used to determine whole-brain volumes from T1-weighted images^{64 65} for analysis of macrostructural brain integrity, as well as FA and MD measures from diffusion-weighted images⁶³ for analysis of microstructural brain integrity. Brain volumes will be corrected for total intracranial volume to account for head size⁶⁶. Reasons for non-completion of MRI scanning will be recorded. Patients will be used as their own controls over time using a within-subjects design.

Sample size

The relationship between cerebral oxygenation during dialysis and delirium in critically ill patients has not been previously explored. We have therefore based our effect size estimate and consequently our sample size on what is clinically relevant for this population, as well as on estimated enrolment rates. 108 subjects will provide 90% power to detect a correlation of 0.3 between two variables, and 90% power to detect a predictor that explains 9% of the remaining variance in a dependent variable of a linear regression model after controlling for other predictors in the model. Given that delirium and long-term neurocognitive trajectories are

multifactorial, and cerebral oxygenation during the first 72 hours of CKRT or during iHD is likely to be a small but highly relevant component of this, these detection limits are clinically meaningful in this population. Approximately five new adult patients are initiated on KRT in the ICU per month at KHSC. Assuming a 90% consent rate based on our prior work, 54 patients per year will be enrolled in the INCOGNITO-AKI study over a two year period, yielding an estimated sample size of 108 patients.

Data management

All information collected from patients will be recorded directly into a Research Electronic Data Capture (REDCap) database housed on the Queen’s University server, which can only be accessed by study team members (<https://fhs.cac.queensu.ca/CNS/>). All patient identifiers will be coded and anonymized. All results from Kinarm and NIRS assessments will be assigned a numeric code associated with each subject and otherwise stripped of all identifying information, and with access restricted to study personnel only. A master linking log connecting patient’s identifiable information (i.e., medical record number) to their study ID will be securely maintained internally behind two locks, with access restricted to study personnel. MRI scans

consisting of a series of DICOM (Digital Image Communication) files will be assigned a numeric code associated with each subject and otherwise stripped of all identifying information using a standard DICOM file anonymizer.

Statistical methods

Primary objectives

The primary objective of this study is the association between intradialytic rSO₂ and delirium during ICU admission, as measured by NIRS. Continuous rSO₂ data throughout each form of dialysis will be summarized using three variables, which together comprise the cerebral perfusion index (CPI): 1) mean rSO₂ throughout dialysis, 2) duration of disturbed cerebral autoregulation, and 3) the area under the curve (AUC) outside of the optimal mean arterial pressure (MAP)⁶⁷. These three summary variables have been used to describe cerebral oxygenation in previous reports^{67 68}.

Mean rSO₂ will be calculated for the duration of oximetry recording during the first CKRT session (1 hour pre-initiation, 72 hours during CKRT, and 1 hour post-cessation, as described

above), and for each iHD session recording period (1 hour pre-initiation, throughout iHD, and for 1 hour post-cessation).

Cerebral autoregulation will be evaluated using the cerebral oximetry index (COx), with time-varying Spearman correlation coefficients calculated between rSO2 values and MAP at one-minute intervals throughout the duration of the oximetry recordings³¹. Positive values of the COx (p<0.0001) are indicative of disturbed cerebral autoregulation³¹. Duration of disturbed cerebral autoregulation will be taken as the length of time during each recording session for which COx values were positive^{67 68}.

Optimal MAP \pm standard deviation (SD) will be calculated as the mean MAP for COx of 0 \pm 1 SD⁶⁷. AUC outside of the optimal MAP will be taken as the proportion of the AUC where AUC was outside of the range of the optimal MAP⁶⁷.

Multiple linear regression using CPI parameters as the independent predictor variables and cumulative CAM-ICU-7 score throughout the patient's ICU stay as the response variable will be

performed. The model will be built from the following potential covariates: age, illness severity
APACHE score, baseline cognition via CDRS, and baseline frailty via CFS.

Secondary objectives

To assess the relationship between rSO₂, delirium, and long-term cognitive impairment, multiple
linear regression will be used to determine association between intradialytic rSO₂ (predictor
variables) and neurocognitive impairment via RBANS/Kinarm scores at 3- and 12-months
(response variables), controlling for covariates (age, frailty, dementia, illness severity, delirium).

Association between rSO₂ values (predictor) and each of brain volume, FA and MD (outcomes)
will be assessed through multiple linear regression. Baseline CDRS score, APACHE score, and
CFS will be included as covariates. Linear regression will be used to determine association
between structural brain pathology (total brain volume, FA, and MD) and neurocognitive
function (RBANS/Kinarm scores), as well as patient well-being (adverse events, MARS, and
MDBQ scores) at 3- and 12-months post-discharge.

Tertiary/exploratory objectives

Our exploratory objective is to assess the differential effect of iHD and CKRT on cerebral oxygenation. To this end, analysis of covariance (ANCOVA) will be used to assess effect of first dialysis modality (iHD vs. CKRT) on integrated intradialytic rSO2 values, while controlling for covariates including baseline hemodynamic status and age. Baseline hemodynamic status will be assessed using information from the APACHE II illness severity scale (i.e., vitals) and RASS score at baseline to evaluate consciousness level. Integrated rSO2 values will be used to determine differential changes from baseline throughout iHD and CKRT.

ETHICS AND DISSEMINATION

This study has been approved by the Queen’s University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board (HSREB), REB approval number: DMED-2424-20. The study protocol does not interfere in any way with the standard of care provided to patients.

Risks of participation

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3 Use of the Kinarm and NIRS are low-risk. There is a risk of incidental findings discovered
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7 by Kinarm. In this event, participants will be referred to a neurologist for further
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10 examination. Results will be communicated to the participant and/or family via a brief written
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13 research report. There is a risk of skin irritation due to the adhesive used in the NIRS device.
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20 MRI is low-risk. No contrast agents (e.g., gadolinium) will be used due to the risk of
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22 nephrogenic systemic fibrosis (NSF) in patients with kidney impairment. There is a risk of
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24 incidental findings discovered by MRI. In this event, participants will be referred to a neurologist
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26 for further examination. Results will be communicated to the participant and/or family via a brief
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37 In spite of our best efforts, if personal health information is inappropriately released, we will take
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39 measures to ensure that further release of information is stopped, that any information which can
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41 be retrieved is retrieved immediately, and that the KHSC and Queen's University Privacy Office
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44 and REB will be notified. Further actions may be taken according to recommendations from the
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Knowledge translation

Prior to study initiation, functional patient-centered outcomes will be sought from diverse patient representatives who have experienced critical illness, and included in the follow-up data collection for the INCOGNITO-AKI study to elucidate meaningful consequences of poor cognition. To inform knowledge translation, these representatives will also be asked for input on how to disseminate and increase accessibility of study results (e.g., multiple languages, print and electronic dissemination, use of text and graphics to represent data, etc.). Results of the INCOGNITO-AKI study will be presented at critical care conferences, and disseminated to ICU patients and families in their preferred method.

Significance

Initiation of acute KRT is increasingly common in critically ill adults admitted to the ICU. This project will provide crucial insight into the early neurological changes occurring in these patients, and their short- and long-term impact on cognitive function. If we discover that cerebral oxygenation is lower when patients are on iHD vs. when they are on CKRT and that this reduction is associated with poorer cognition and neuroimaging findings, this will provide a

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3 rationale for developing a protocol to maximize rSO₂ and control ultrafiltration rate during iHD.
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7 This understanding will further serve as a foundation for developing interventions to improve
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10 neurological outcomes in this vulnerable cohort, thereby reducing their overall morbidity and
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13 mortality and relieving stress on an already burdened healthcare system.
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For peer review only

AUTHOR CONTRIBUTIONS

JG Boyd and NA Jawa designed the study and wrote the study protocol. NA Jawa drafted and revised the manuscript. JG Boyd, RM Holden, SA Silver, BYM Kwan, PA Norman, AG Day, DM Maslove, J Muscedere, and SH Scott reviewed and revised the manuscript. SH Scott developed, designed and manages the Kinarm robotic labs that will be used in the INCOGNITO-AKI study.

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COMPETING INTERESTS STATEMENT

SH Scott is co-founder and CSO of Kinarm that commercializes the Kinarm robotic technology used in the present study. NA Jawa, RM Holden, SA Silver, AG Day, PA Norman, BYM Kwan, DM Maslove, J Muscedere, and JG Boyd have no conflicts of interest to declare.

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68. Wood MD, Khan J, Lee KFH, et al. Assessing the relationship between near-infrared spectroscopy-derived regional cerebral oxygenation and neurological dysfunction in critically ill adults: a prospective observational multicentre protocol, on behalf of the Canadian Critical Care Trials Group. *BMJ Open* 2019;9(6):e029189. doi: 10.1136/bmjopen-2019-029189 [published Online First: 2019/06/28]

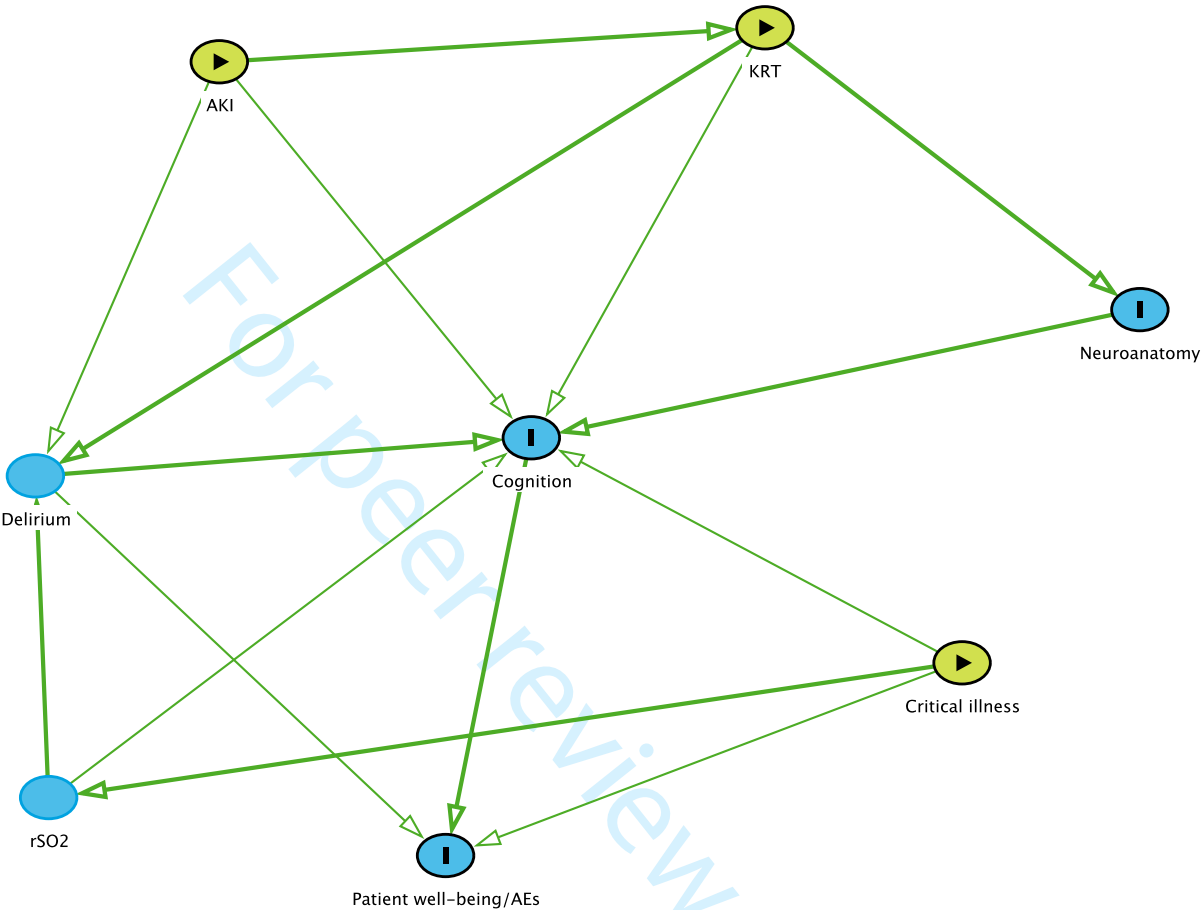
FIGURE LEGENDS

Figure 1. Hypothesized causal pathway.

Figure 2. Study schema.

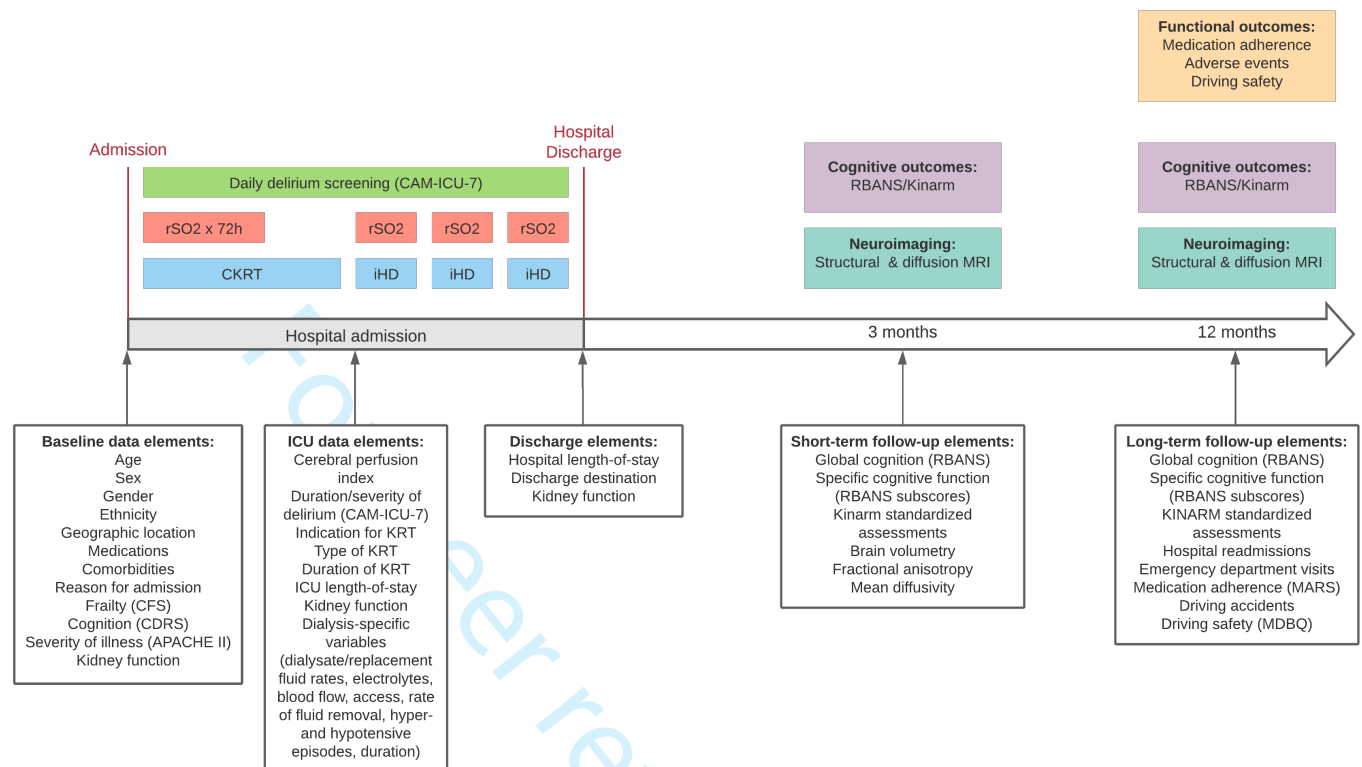
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Figure 1. Hypothesized causal pathway.



Green arrows represent causal paths; blue circles represent ancestors of outcome variables; blue circles with a line represent outcome variables; green circles with a triangle represent exposures. Cerebral oxygenation (rSO2); acute kidney injury (AKI); kidney replacement therapy (KRT); adverse events (AEs).

Figure 2. Study schema.



Cerebral oxygenation (rSO₂); kidney replacement therapy (KRT); continuous KRT (CKRT); intermittent hemodialysis (iHD); Clinical Frailty Scale (CFS); Clinical Dementia Rating Scale (CDRS); Acute Physiological Assessment and Chronic Health Evaluation (APACHE II); Confusion Assessment Method-ICU-7 (CAM-ICU-7); Repeatable Battery for the Assessment of Neuropsychological Status (RBANS); Medication Adherence Rating Scale (MARS); Manchester Driver Behaviour Questionnaire (MDBQ).

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

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			Page
Reporting Item			Number
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	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	24
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 24

1	Roles and	#5b	Name and contact information for the trial sponsor	N/A
2	responsibilities:			
3	sponsor contact			
4	information			
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7	Roles and	#5c	Role of study sponsor and funders, if any, in study design;	N/A
8	responsibilities:		collection, management, analysis, and interpretation of data;	
9	sponsor and funder		writing of the report; and the decision to submit the report for	
10			publication, including whether they will have ultimate	
11			authority over any of these activities	
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14	Roles and	#5d	Composition, roles, and responsibilities of the coordinating	N/A
15	responsibilities:		centre, steering committee, endpoint adjudication committee,	
16	committees		data management team, and other individuals or groups	
17			overseeing the trial, if applicable (see Item 21a for data	
18			monitoring committee)	
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24	Introduction			
25				
26	Background and	#6a	Description of research question and justification for	6-11
27	rationale		undertaking the trial, including summary of relevant studies	
28			(published and unpublished) examining benefits and harms for	
29			each intervention	
30				
31				
32				
33	Background and	#6b	Explanation for choice of comparators	N/A
34	rationale: choice of			
35	comparators			
36				
37				
38	Objectives	#7	Specific objectives or hypotheses	11-12
39				
40	Trial design	#8	Description of trial design including type of trial (eg, parallel	
41			group, crossover, factorial, single group), allocation ratio, and	
42			framework (eg, superiority, equivalence, non-inferiority,	
43			exploratory)	
44				
45				
46				
47				
48	Methods:			
49	Participants,			
50	interventions, and			
51	outcomes			
52				
53				
54	Study setting	#9	Description of study settings (eg, community clinic, academic	12-13
55			hospital) and list of countries where data will be collected.	
56			Reference to where list of study sites can be obtained	
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1	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)	13
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6	Interventions:	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	14-18
7	description			
8				
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10	Interventions:	#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)	14
11	modifications			
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17	Interventions:	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	14
18	adherence			
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22	Interventions:	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
23	concomitant care			
24				
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26	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	15-18
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37	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)	13-18; Figure 2
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43	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	18
44				
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48	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	13, 18
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52	Methods:			
53	Assignment of			
54	interventions (for			
55	controlled trials)			
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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; not a controlled trial
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; not a controlled trial
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A; not a controlled trial
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A; not a controlled trial
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A; not a controlled trial
Methods: Data collection, management, and analysis			
Data collection plan	#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	14-15
Data collection plan: retention	#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	16, 18

1	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	18-19
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9	Statistics: outcomes	#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	19-21
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14	Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	21
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18	Statistics: analysis population and missing data	#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)	N/A
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24	Methods: Monitoring			
25				
26	Data monitoring: formal committee	#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
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36	Data monitoring: interim analysis	#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
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41	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	N/A
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46	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
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52	Ethics and dissemination			
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56	Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	21
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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)	13-14
Consent or assent: ancillary studies	#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	18-19
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	24
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18-19
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: trial results	#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	22
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	N/A

1	Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of	N/A
2			biological specimens for genetic or molecular analysis in the	
3			current trial and for future use in ancillary studies, if	
4			applicable	
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8	None The SPIRIT checklist is distributed under the terms of the Creative Commons Attribution License CC-			
9	BY-ND 3.0. This checklist can be completed online using https://www.goodreports.org/ , a tool made by the			
10	EQUATOR Network in collaboration with Penelope.ai			
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BMJ Open

Identifying neurocognitive outcomes and cerebral oxygenation in critically ill adults on acute kidney replacement therapy in the intensive care unit: The INCOGNITO-AKI study protocol

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Title: Identifying neurocognitive outcomes and cerebral oxygenation in critically ill adults on acute kidney replacement therapy in the intensive care unit: The INCOGNITO-AKI study protocol

Authors: Natasha A. Jawa¹, Rachel M. Holden², Samuel A. Silver², Stephen H. Scott^{1,3,4}, Andrew G. Day^{5,6}, Patrick A. Norman⁵, Benjamin Y. M. Kwan⁷, David M. Maslove^{8,9}, John Muscedere^{8,9}, J. Gordon Boyd^{1,4,8,9}

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Registration: clinicaltrials.gov, registration number (pending)

Protocol version: 2.1; July 22, 2021

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ABSTRACT

Introduction. Initiation of acute kidney replacement therapy (KRT) is common in critically ill adults admitted to the intensive care unit (ICU), and associated with increased morbidity and mortality. KRT has been linked to poor neurocognitive outcomes, leading to reduced quality of life, and increased utilization of healthcare resources. Adults on dialysis in the ICU may be particularly at risk of neurocognitive impairment, as survivors of critical illness are already predisposed to developing cerebrovascular disease and cognitive dysfunction long-term relative to healthy controls. Regional cerebral oxygen saturation (rSO2) may provide a critical early marker of long-term neurocognitive impairment in this population. This study aims to understand cerebral oxygenation in patients undergoing KRT (continuous or intermittent) in the ICU. These findings will be correlated with long-term cognitive and functional outcomes, and structural brain pathology.

Methods and analysis. 108 patients scheduled to undergo treatment for acute kidney injury with KRT in the Kingston Health Sciences Centre ICU will be recruited into this prospective

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4 observational study. Enrolled patients will be assessed with intradialytic cerebral oximetry using
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7 near infrared spectroscopy (NIRS). Delirium will be assessed daily with the Confusion
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10 Assessment Method-Intensive Care Unit (CAM-ICU) and severity quantified as cumulative
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13 CAM-ICU-7 scores. Neurocognitive impairment will be assessed at 3- and 12-months after
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16 hospital discharge using the Kinarm and Repeatable Battery for the Assessment of
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19 Neuropsychological Status (RBANS). Structural brain pathology on MRI will also be measured
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22 at the same timepoints. Driving safety, adverse events, and medication adherence will be
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25 assessed at 12-months to evaluate the impact of neurocognitive impairment on functional
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28 outcomes.
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37 **Ethics and dissemination.** This study is approved by the Queen's University Health
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40 Sciences/Affiliated Teaching Hospitals Research Ethics Board (DMED-2424-20). Results will be
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43 presented at critical care conferences, and a lay summary will be provided to patients in their
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46 preferred format.
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54 **Trial registration number.** NCT04722939.
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ARTICLE SUMMARY

Strengths and limitations of this study:

- This will be the first study to use a comprehensive battery of neurological tests to interrogate both short- and long-term neurological impairment in critically ill adults on dialysis
- This study will employ robotic technology in a novel patient population to provide a quantitative assessment of neurocognitive function across a range of cognitive domains
- The targeted sample size will permit statistically powered conclusions to be drawn from primary analyses
- The study protocol will be conducted at a single centre

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4 INTRODUCTION

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10 Due to advances in critical care, the number of individuals surviving critical illness has increased

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13 significantly over the past two decades. This increased survivorship has led to recognition of

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17 post-intensive care unit (ICU) syndrome, characterized by long-term cognitive, psychological,

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20 and functional limitations¹. For example, one year following ICU admission, survivors have

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23 cognitive performance similar to individuals with mild dementia or moderate traumatic brain

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26 injury². These impairments have important implications for quality of life, as only approximately

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29 two-thirds of previously employed individuals ever return to work following their ICU stay^{3 4}.

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34 The underlying cause of this cognitive impairment after critical illness is unclear, although it is

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37 known that delirium is one of the most consistent risk factors for long-term cognitive

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40 impairment⁵.

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47 Delirium is an acute change in level of consciousness, characterized by impaired attention and

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50 disorganized thinking, affecting up to 80% of critically ill patients⁶. Our group has demonstrated

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54 that low cerebral oxygenation, as measured by near-infrared spectroscopy (NIRS), is an

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independent risk factor for delirium in critically ill patients⁷. However, delirium is clearly multifactorial, and other key risk factors have also been described, including acute kidney injury (AKI)⁸.

The incidence of severe AKI is on the rise, with up to 13% of adults admitted to ICUs per year requiring kidney replacement therapy (KRT⁹)¹⁰⁻¹². Outpatient KRT in the form of intermittent hemodialysis (iHD) and peritoneal dialysis (PD) has been linked to poor neurocognitive outcomes due to vascular and metabolic disturbances¹³, and adults initiated on dialysis in the ICU may be particularly at risk due to their superimposed critical illness.

The goal of this study is to examine the relationship between KRT, delirium, and long-term structural and cognitive outcomes in critically ill patients. We urgently need the results of such studies to reveal risk factors for poor cognitive and neurological outcomes in patients treated with KRT after ICU discharge, and to inform how different KRT modalities affect cognitive function in these vulnerable patients.

Overall Hypothesis

We hypothesize that KRT is associated with low cerebral oxygenation, which in turn will be associated with delirium and long-term structural and functional neurological consequences at 3- and 12-months. We further hypothesize that iHD is a risk factor for lower cerebral oxygenation relative to CKRT, due to rapid hemodynamic shifts. These impairments will have negative effects on patient quality of life.

Kidney Replacement Therapy in the ICU

The decision to initiate KRT in patients admitted to the ICU is largely driven by medically refractory fluid overload, uremia, electrolyte disturbances, or metabolic acidosis, often in the setting of severe AKI (¹⁴). The burden of dialysis-requiring AKI is rising^{15 16}, particularly among critically ill adults¹⁵. Over half of all adults admitted to the ICU will develop AKI¹¹, with 3-13% ultimately requiring treatment with KRT¹². The risk of acquiring AKI among hospitalized or critically ill patients further increases with age and the presence of other comorbid conditions including chronic kidney disease, heart disease, hypertension, diabetes, dementia, and cancer¹⁷.

Three modalities of KRT are available for use in the acute setting: iHD, continuous KRT (CKRT), and PD, with the former two being the most frequently used in patients admitted to the ICU¹⁸. iHD provides the most efficient clearance, but is poorly tolerated in hemodynamically unstable patients (e.g., those requiring hemodynamic support with vasopressors)¹⁹. CKRT uses slower rates of blood and dialysate flow over longer time periods, and is consequently more amenable to use in unstable populations²⁰. Many patients started on CKRT are often later transitioned to iHD as they become more capable of tolerating rapid hemodynamic shifts. However, unlike CKRT in which the brain's ability to regulate blood flow in response to changing blood pressures (cerebral autoregulation) appears to be unperturbed²¹, the rapid shifts during iHD are known to affect cerebral perfusion²². No studies to date have explored the implications of dialysis or of transitioning from CKRT to iHD on cerebral perfusion.

rSO₂ as a surrogate marker of cerebral perfusion during critical illness and kidney replacement therapy

Regional cerebral oxygen saturation (rSO₂) in the frontal cortex—a surrogate marker of overall brain oxygenation—is a reliable marker of cerebral perfusion²³ and can be used to evaluate

cerebral autoregulation²⁴. rSO₂ can be measured in critically ill patients using near-infrared spectroscopy (NIRS), in which a light sensor placed on the patient's forehead is used to non-invasively assess the oxygenation level of hemoglobin in the underlying brain tissue²⁵. Cerebral blood flow and rSO₂ are reduced in adults with end-stage kidney disease (ESKD) undergoing *long-term* maintenance dialysis²⁶, and have been associated with poor cognitive outcomes²⁷⁻²⁹. Moreover, low rSO₂ in other populations has been correlated with neurological abnormalities on brain imaging³⁰. Still, longitudinal studies examining the consequences of *short-term* acute dialysis on rSO₂ and its relationship with long-term cognitive function and neuroimaging have yet to be undertaken.

Rapid changes in mean arterial pressure (MAP) during iHD are generally well tolerated among stable individuals in the ICU, and providers have traditionally operated under the assumption that cerebral autoregulation is unperturbed by these rapid hemodynamic shifts. However, recent data from our group has demonstrated that cerebral autoregulation is disturbed in critically ill patients not undergoing dialysis³¹. An understanding of the consequences of dialysis on cerebral

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4 autoregulation in critically ill patients is needed to guide decision-making regarding choice of
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7 KRT modality in the ICU.
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13 **Neurocognitive outcomes of AKI**

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17 AKI is associated with an increased risk for long-term neurological issues, including
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20 inflammation, stroke, delirium, and cognitive deficits, including dementia³²⁻³⁵. Prior research by
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23 our group has further demonstrated that survivors of AKI experience quantifiable deficits in the
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26 areas of attention, visuomotor, and executive function³⁶.
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33 **Neurocognitive outcomes of KRT**

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37 Maintenance dialysis is associated with short- and long-term neurocognitive impairment,
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40 including a decline in executive function³⁷⁻⁴⁰. Up to 70% of patients undergoing maintenance
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43 iHD demonstrate cognitive impairment⁴¹. Studies in patients with chronic kidney disease (CKD)
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46 have posited that for every 10 mL/min/1.73m² decline in estimated glomerular filtration rate
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49 (eGFR) below 60 mL/min/1.73m², an 11% increased prevalence of cognitive dysfunction
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52 occurs⁴². This decline is further pronounced in individuals with CKD undergoing treatment with
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dialysis, due to their increased risk for cerebrovascular disease^{27 43}. Despite this understanding of the cognitive outcomes of kidney dysfunction and KRT in the chronic setting, the neurocognitive impact of acute KRT remains largely unknown, and cognition has seldom been the focus of KRT trials in the ICU.

Patients on iHD may be particularly vulnerable to adverse neurocognitive effects, as a result of the rapid hemodynamic shifts that occur during treatment. To this end, cognitive fluctuations have been noted as a consequence of iHD, including deterioration in cognitive function post-iHD compared with pre-iHD levels, particularly in areas of attention and executive function⁴⁴.

Kidney disease and critical illness independently predict long-term structural brain pathology

Adults with CKD exhibit structural neurological changes on neuroimaging. eGFR has been inversely associated with white matter microstructural integrity in a diffusion tensor imaging (DTI) study of the brain, as evidenced by lower fractional anisotropy (FA) and higher mean diffusivity (MD) in healthy controls⁴⁵. Furthermore, CKD has been linked to global brain

atrophy, demonstrated by increased lateral ventricle and sulci dilation⁴⁶, and reduced white matter volume⁴⁷.

Additional neuroimaging findings have been found in those with CKD on dialysis. White matter hyperintensities are more prevalent in patients on iHD relative to their healthy counterparts⁴⁸, and those on iHD have an increased ventricular-brain ratio relative to healthy controls⁴⁹.

ICU survivors show a similar increase in ventricle-brain ratio suggestive of cerebral atrophy compared to age-matched controls⁵⁰. In the same study, the authors found a correlation between duration of delirium and degree of frontal and temporal lobe atrophy⁵⁰. It is not clear whether any patients in that study had CKD, AKI or required CKRT.

Study aims and hypotheses

1. Impact of dialysis on rSO₂ and delirium

Patients on maintenance dialysis experience an intradialytic reduction in cerebral oxygenation²³. Reduced cerebral oxygenation in other contexts in the ICU is known to be associated with delirium⁷. The effect of dialysis on rSO₂, and the effect of intradialytic rSO₂ on delirium in the ICU is unknown. We hypothesize that patients undergoing KRT will demonstrate an intradialytic drop in rSO₂ from baseline, and that more pronounced reductions in rSO₂ will be associated with increased severity of delirium. We further hypothesize that lower intradialytic rSO₂, longer durations of disturbed cerebral autoregulation, and larger areas under the curve (AUC) outside of patient's optimal mean arterial pressure (MAP) will be associated with increased severity of delirium.

2. Long-term consequences of intradialytic rSO₂ at 3- and 12-months post-ICU discharge

The long term impact of alterations in cerebral oxygenation during acute dialysis are unknown. We hypothesize that intradialytic rSO₂ during acute dialysis will be correlated with reduced neurocognitive function at 3- and 12-months after ICU discharge, and that patients with worse delirium scores will exhibit greater cognitive dysfunction. We further hypothesize that cognitive

impairment at 3- and 12-months will be associated with an increased risk for poorer adherence to treatment regimens, adverse events, and increased rate of driving accidents⁵¹.

Poor kidney function is associated with structural neurological impairment in patients with CKD and on maintenance dialysis. Low cerebral oxygenation and delirium are independently correlated with neurological abnormalities on imaging. The effect of dialysis and rSO₂ during critical illness on structural neuroanatomy is unknown. We hypothesize that severe, prolonged delirium and lower rSO₂ during dialysis in the ICU are associated with structural neurological impairment at a macro- and micro-structural level.

3. Differential effects of different dialysis modalities on rSO₂

Patients on maintenance dialysis exhibit lower rSO₂ during dialysis sessions²³; the impact of short-term dialysis on rSO₂ is unknown. We hypothesize that iHD is a risk factor for lower rSO₂ vs. CKRT, due to rapid hemodynamic shifts.

Hypothesized causal pathway

The hypothesized causal pathway is outlined in *Figure 1*. AKI resulting in the receipt of KRT will lead to a reduction in cerebral oxygenation from baseline. This reduced cerebral oxygenation will be associated with an increased risk for delirium. Downstream consequences of low cerebral oxygenation and delirium will include reduced brain structural integrity (as evidenced by high mean diffusivity [MD] and low fractional anisotropy [FA]), increased brain atrophy, reduced cognitive function, and reduced patient well-being, (evidenced by a lower ability to adhere to prescribed medication regimens, and reduced driving safety).

METHODS AND ANALYSIS

Patient and public involvement

Patient representatives who have experienced critical illness will be sought prior to study initiation, to inform both patient-centered long-term outcome data collection as well as knowledge dissemination.

Study design and setting

This is a prospective, observational cohort study of critically ill participants initiated on acute KRT (iHD or CKRT). The INCOGNITO-AKI study will take place in a 33-bed medical-surgical intensive care unit at a tertiary academic hospital in Ontario, Canada.

Eligibility criteria

The inclusion criteria for the INCOGNITO-AKI study are: age greater than or equal to 18 years; admitted to the KHSC ICU; diagnosis of severe AKI requiring KRT (defined by the presence of either a twofold increase in serum creatinine from baseline, serum creatinine level greater than or equal to 354 $\mu\text{mol/L}$ with an increase of 27 $\mu\text{mol/L}$ from baseline, or urine output <6 mL/kg in the preceding 12 hours⁵²); and within 12 hours of initiation of KRT via iHD or CKRT.

Patients will be excluded from the study if they have acquired or congenital neurological disorders; any contraindication to testing with cerebral oximetry, Kinarm, or MRI (e.g., claustrophobia, limb amputation, paresis, neuromuscular disorders, etc.); KRT via PD; failure to consent; life expectancy less than 24 hours; clinical suspicion of renal obstruction, rapidly

progressive glomerulonephritis or interstitial nephritis; or prehospitalization eGFR <30 mL/min/1.73m².

Recruitment and consent

Patients will be screened for eligibility and recruited by the research team from the KHSC ICU within 12 hours of initiation of KRT. Patients will be evaluated for capacity to consent on an ongoing basis. If unable to consent individually, consent will be obtained from the participant’s substitute decision maker.

Participants will be informed of their right to withdraw from the study at any time. Should a participant feel claustrophobic within the MRI or Kinarm robotic device during any of the assessments, or experience any other perceived or real adverse symptoms, the assessment will be stopped immediately, and the participant will be given the option of reattempting the assessment at a later date or withdrawing from the study altogether.

To facilitate recruitment and retention, compensation for time and travel will be provided.

Follow-up visits will be scheduled when patients are already returning to KHSC for clinical care, and will be offered at flexible times. Recruitment materials will represent the diverse spectrum of age, sex, and gender within the critical care population.

Upon consent, participants will undergo a variety of assessments in accordance with the INCOGNITO-AKI Study Schema (*Figure 2*). Assessments will be obtained purely for investigational purposes and will not alter the patient's treatment in any way.

Data collection

Patients admitted to the KHSC ICU receiving KRT will be enrolled within 12 hours of KRT initiation (ideally within 6 hours). Reasons for exclusion of screened but ineligible participants will be recorded. Baseline data including demographic information (age, sex, gender, ethnicity, geographic location [first 3 digits of postal code]), medications (including antihypertensive medications), comorbidities (including hypertension and history of mental illness e.g., depression, anxiety), reason for ICU admission, frailty (assessed by Clinical Frailty Scale, CFS),

baseline cognition (Clinical Dementia Rating Scale, CDRS) and illness severity (assessed via Acute Physiological Assessment and Chronic Health Evaluation, APACHE II) will be collected from patient’s medical records and via self-report.

Delirium will be assessed daily during ICU admission using the Confusion Assessment Method (CAM)-ICU-7 delirium severity scale⁵³, which requires daily assessment using the Richmond Agitation Sedation Scale (RASS) to quantify patients’ level of sedation/consciousness.

Additional ICU-specific data elements will be collected, including indication for dialysis, type of KRT (iHD vs. CKRT, if CKRT then CVVH vs. CVVHD vs. CVVHDF), indication for type of KRT, kidney function, dialysis-specific variables (dialysate/replacement fluid rates, electrolytes, access, blood flow, rate of fluid removal, hyper- and hypotensive episodes, duration of treatment, type of anticoagulation), duration of KRT, and ICU length-of-stay.

At time of hospital discharge, hospital length-of-stay, discharge destination, kidney function (eGFR), and ongoing maintenance dialysis requirements will be recorded.

During participants' 3- and 12-month follow-up visits, information on their maintenance dialysis requirements, as well as their most recent laboratory data for creatinine/eGFR, will be recorded.

Outcomes

Cerebral oximetry

Cerebral oxygenation can be continuously monitored with non-invasive oximeters employing NIRS to generate rSO₂ values⁵⁴. Participants on CKRT will undergo continuous cerebral oximetry using the CASMED FORESIGHT Elite cerebral oximeter (Edwards LifeSciences, USA) during the first 72 hours of CKRT. Post-CKRT oximetry will be measured for 1 hour following completion of CKRT. Participants on iHD will undergo oximetry beginning 1 hour prior to each iHD session, continuously throughout each session, and ending 1 hour following completion of each session.

Neurocognitive testing

Kinarm

Kinarm End-Point Lab (Kinarm, Kingston, Canada), is an interactive robotic technology that uses a battery of behavioural tasks, called Kinarm Standard Tests (KST), that precisely quantifies sensory, motor, and neurocognitive impairment⁵⁵. Our group has previously demonstrated the feasibility of using the Kinarm for neurocognitive assessment in ICU survivors⁵⁶. Participants will undergo serial Kinarm assessment at 3- and 12-months after discharge. Reasons for non-completion of Kinarm assessments will be recorded.

The specific Kinarm tasks to be used in the INCOGNITO-AKI study are outlined in *Table 1*.

Table 1. Kinarm tasks and domains of neurocognitive function assessed in the INCOGNITO-AKI study.

Task	Task type	Neurocognitive domain
Arm position matching	Sensorimotor	Somatosensory processing for perception, position-sense
Ball on bar	Sensorimotor	Bi-manual coordination, visuomotor skills
Visually guided reaching	Sensorimotor	Motor coordination, visuomotor skills, postural control of arm

Reverse visually guided reaching	Cognitive-motor	Visuomotor skills, cognitive ability to override automatic motor responses
Object hit	Cognitive-motor	Rapid visuomotor skills, bi-manual motor planning, spatial attention
Object hit and avoid	Cognitive-motor	Rapid motor decisions, bi-manual motor planning, spatial attention, executive function (attention and inhibitory control)
Trails A&B	Sensory-cognitive	Executive function, task switching
Paired Associate Learning	Sensory-cognitive	Visuospatial working memory

Adapted from the Kinarm user guide⁵⁷.

All Kinarm task-specific parameters will be standardized to available normative control data generated as part of the validation process for the Kinarm robot, accounting for age, sex, handedness, and Kinarm platform effects⁵⁷. Task-specific parameter values are then summed to generate global task scores for each participant, providing an assessment of overall performance on a given task. All scores will be normalized to *z*-scores. Neurocognitive impairment in the INCOGNITO-AKI study will be defined as a task *z*-score greater than the 95th percentile (i.e., *z*-scores greater than 1.64 indicate impairment on the given task relative to the healthy control

cohort used to validate KST), in accordance with previously published literature using the Kinarm robot⁵⁸.

Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)

Global cognition will be assessed using the RBANS at the same time points. The RBANS is a 30-minute tool used to screen and quantify cognitive impairment in adults, across a variety of domains⁵⁹, and is commonly used to assess cognition in ICU survivors. Neurocognitive domains assessed through the RBANS include immediate and delayed memory, visuospatial/constructional, language, and attention⁵⁹.

Functional outcomes

Functional patient outcomes will be assessed at 12-months after discharge, and will include assessment of medication adherence using the Medication Adherence Rating Scale (MARS); assessment of adverse events including number of re-hospitalizations and emergency department visits; and driving safety (number of motor vehicle accidents, and Manchester Driver Behavior Questionnaire).

Structural neuroimaging

Patients will undergo serial structural magnetic resonance imaging (MRI) of the brain at 3- and 12-months after discharge. Anonymized and de-identified MRI scans will be processed using MIPAV⁶⁰ v.7.3.0 and Oxford Centre for Functional MRI of the Brain (FMRIB) Software Library (FSL)⁶¹ v.5.0 medical image processing programs. Scans will be corrected for intensity non-uniformity⁶² and transformed into a common image space to adjust for variations in head size and orientation⁶³. Skull stripping will be performed⁶⁴. Automated and semi-automated techniques will be used to determine whole-brain volumes from T1-weighted images^{64 65} for analysis of macrostructural brain integrity, as well as FA and MD measures from diffusion-weighted images⁶³ for analysis of microstructural brain integrity. Brain volumes will be corrected for total intracranial volume to account for head size⁶⁶. Reasons for non-completion of MRI scanning will be recorded. Patients will be used as their own controls over time using a within-subjects design.

Sample size

The relationship between cerebral oxygenation during dialysis and delirium in critically ill patients has not been previously explored. However, previous research by our group has demonstrated a correlation of 0.34 between cerebral oximetry parameters (i.e., dysfunctional

cerebral autoregulation) and delirium in critically ill adults. Assuming a similar correlation will be found through the present study, then 93 patients would be needed to detect a correlation of 0.34 at a two-sided 0.05 significance level with 90% power. Given that we do not know what the correlation in critically ill patients on KRT will be, we have based our effect size estimate and consequently our sample size on what is clinically relevant for this population, as well as on estimated enrolment rates. 108 subjects will provide 90% power to detect a correlation of 0.3 between two variables, and 90% power to detect a predictor that explains 9% of the remaining variance in a dependent variable of a linear regression model after controlling for other predictors in the model. Given that delirium and long-term neurocognitive trajectories are multifactorial, and cerebral oxygenation during the first 72 hours of CKRT or during iHD is likely to be a small but highly relevant component of this, these detection limits are clinically meaningful in this population. Approximately five new adult patients are initiated on KRT in the ICU per month at KHSC. Assuming a 90% consent rate based on our prior work, 54 patients per year will be enrolled in the INCOGNITO-AKI study over a two year period, yielding an estimated sample size of 108 patients.

Data management

All information collected from patients will be recorded directly into a Research Electronic Data Capture (REDCap) database housed on the Queen's University server, which can only be accessed by study team members (<https://fhs.cac.queensu.ca/CNS/>). All patient identifiers will be coded and anonymized. All results from Kinarm and NIRS assessments will be assigned a numeric code associated with each subject and otherwise stripped of all identifying information, and with access restricted to study personnel only. A master linking log connecting patient's identifiable information (i.e., medical record number) to their study ID will be securely maintained internally behind two locks, with access restricted to study personnel. MRI scans consisting of a series of DICOM (Digital Image Communication) files will be assigned a numeric code associated with each subject and otherwise stripped of all identifying information using a standard DICOM file anonymizer.

Statistical methods

Primary objectives

The primary objective of this study is the association between intradialytic rSO₂ and delirium during ICU admission, as measured by NIRS. Continuous rSO₂ data throughout each form of

dialysis will be summarized using four variables, which together comprise the cerebral perfusion index (CPI): 1) mean intradialytic rSO₂, 2) delta-rSO₂, 3) duration of disturbed cerebral autoregulation, and 3) AUC outside of the optimal MAP⁶⁷. These four summary variables have been used to describe cerebral oxygenation in previous reports⁶⁷⁻⁶⁹.

Mean intradialytic rSO₂ will be calculated for the duration of oximetry recording during the first CKRT session (72 hours during CKRT, as described above), and for each iHD session recording period. Mean intradialytic rSO₂ will be calculated as the mean rSO₂ of all total KRT minutes, irrespective of whether the patient has been initiated on CKRT, iHD, or a combination thereof.

Delta-rSO₂ will be calculated as the absolute difference between the mean intradialytic rSO₂ (as described above) and the mean baseline rSO₂, where mean baseline rSO₂ is defined as the mean rSO₂ during the 1-hour oximetry recording pre-initiation of CKRT, or the mean rSO₂ during the 1-hour oximetry recording pre-initiation of each iHD session.

Cerebral autoregulation will be evaluated using the cerebral oximetry index (COx), with time-varying Spearman correlation coefficients calculated between rSO₂ values and MAP at one-minute intervals throughout the duration of the oximetry recordings³¹. Positive values of the COx (p<0.0001) are indicative of disturbed cerebral autoregulation³¹. Cumulative duration of disturbed cerebral autoregulation will be taken as the length of time during each recording session for which COx values were positive^{67 68}. Duration of disturbed cerebral autoregulation will be taken as the percentage of total recording time during which cerebral autoregulation was disturbed (i.e., the cumulative duration of cerebral autoregulation dysfunction will be divided by the total recording time and then multiplied by 100 to calculate the percentage of time with cerebral autoregulation dysfunction)³¹.

Optimal MAP \pm standard deviation (SD) will be calculated as the mean MAP for COx of 0 \pm 1 SD⁶⁷. AUC outside of the optimal MAP will be taken as the proportion of the AUC where AUC was outside of the range of the optimal MAP⁶⁷.

Multiple linear regression using the four CPI parameters as the independent predictor variables and cumulative CAM-ICU-7 score throughout the patient’s ICU stay as the response variable will be performed. The model will be built from the following potential covariates: age, illness severity APACHE score, baseline cognition via CDRS, and baseline frailty via CFS.

Secondary objectives

To assess the relationship between rSO2, delirium, and long-term cognitive impairment, multiple linear regression will be used to determine association between CPI parameters (predictor variables) and neurocognitive impairment via RBANS/Kinarm scores at 3- and 12-months (response variables), controlling for covariates (age, frailty, dementia, illness severity, delirium).

Association between rSO2 values (predictor) and each of brain volume, FA and MD (outcomes) will be assessed through multiple linear regression. Baseline CDRS score, APACHE score, and CFS will be included as covariates. Linear regression will be used to determine association between structural brain pathology (total brain volume, FA, and MD) and neurocognitive

function (RBANS/Kinarm scores), as well as patient well-being (adverse events, MARS, and MDBQ scores) at 3- and 12-months post-discharge.

Tertiary/exploratory objectives

Our exploratory objective is to assess the differential effect of iHD and CKRT on cerebral oxygenation. To this end, analysis of covariance (ANCOVA) will be used to assess effect of first dialysis modality (iHD vs. CKRT) on integrated intradialytic rSO₂ values, while controlling for covariates including baseline hemodynamic status and age. Baseline hemodynamic status will be assessed using information from the APACHE II illness severity scale (i.e., vitals) and RASS score at baseline to evaluate consciousness level. Integrated rSO₂ values will be used to determine differential changes from baseline throughout iHD and CKRT.

ETHICS AND DISSEMINATION

This study has been approved by the Queen’s University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board (HSREB), REB approval number: DMED-2424-20.

The study protocol does not interfere in any way with the standard of care provided to patients.

Risks of participation

Use of the Kinarm and NIRS are low-risk. There is a risk of incidental findings discovered by Kinarm. In this event, participants will be referred to a neurologist for further examination. Results will be communicated to the participant and/or family via a brief written research report. There is a risk of skin irritation due to the adhesive used in the NIRS device.

MRI is low-risk. No contrast agents (e.g., gadolinium) will be used due to the risk of nephrogenic systemic fibrosis (NSF) in patients with kidney impairment. There is a risk of incidental findings discovered by MRI. In this event, participants will be referred to a neurologist for further examination. Results will be communicated to the participant and/or family via a brief written research report.

In spite of our best efforts, if personal health information is inappropriately released, we will take measures to ensure that further release of information is stopped, that any information which can be retrieved is retrieved immediately, and that the KHSC and Queen's University Privacy Office and REB will be notified. Further actions may be taken according to recommendations from the Privacy Office and REB.

Knowledge translation

Prior to study initiation, functional patient-centered outcomes will be sought from diverse patient representatives who have experienced critical illness, and included in the follow-up data collection for the INCOGNITO-AKI study to elucidate meaningful consequences of poor cognition. To inform knowledge translation, these representatives will also be asked for input on how to disseminate and increase accessibility of study results (e.g., multiple languages, print and electronic dissemination, use of text and graphics to represent data, etc.). Results of the INCOGNITO-AKI study will be presented at critical care conferences, and disseminated to ICU patients and families in their preferred method.

Significance

Initiation of acute KRT is increasingly common in critically ill adults admitted to the ICU. This project will provide crucial insight into the early neurological changes occurring in these patients, and their short- and long-term impact on cognitive function. If we discover that cerebral oxygenation is lower when patients are on iHD vs. when they are on CKRT and that this reduction is associated with poorer cognition and neuroimaging findings, this will provide a rationale for developing a protocol to maximize rSO2 and control ultrafiltration rate during iHD. This understanding will further serve as a foundation for developing interventions to improve neurological outcomes in this vulnerable cohort, thereby reducing their overall morbidity and mortality and relieving stress on an already burdened healthcare system.

AUTHOR CONTRIBUTIONS

JG Boyd and NA Jawa designed the study and wrote the study protocol. NA Jawa drafted and revised the manuscript. JG Boyd, RM Holden, SA Silver, BYM Kwan, PA Norman, AG Day, DM Maslove, J Muscedere, and SH Scott reviewed and revised the manuscript. SH Scott developed, designed and manages the Kinarm robotic labs that will be used in the INCOGNITO-AKI study.

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COMPETING INTERESTS STATEMENT

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SH Scott is co-founder and CSO of Kinarm that commercializes the Kinarm robotic technology used in the present study. NA Jawa, RM Holden, SA Silver, AG Day, PA Norman, BYM Kwan, DM Maslove, J Muscedere, and JG Boyd have no conflicts of interest to declare.

WORD COUNT

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For peer review only

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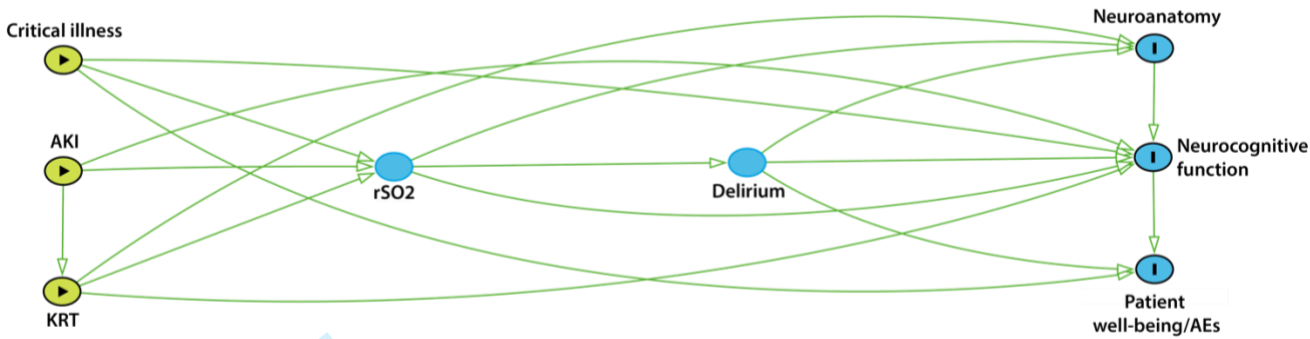
FIGURE LEGENDS

Figure 1. Hypothesized causal pathway.

Figure 2. Study schema.

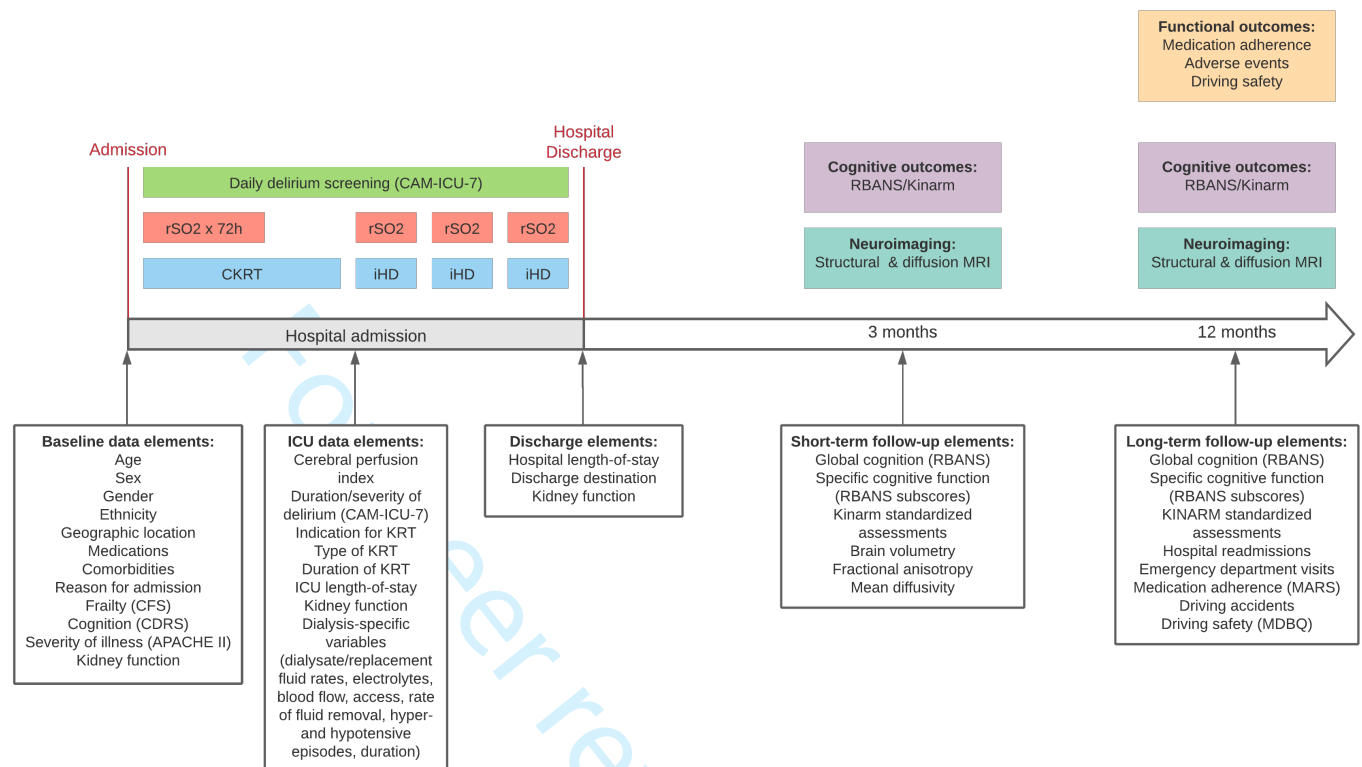
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Figure 1. Hypothesized causal pathway.



Green arrows represent causal paths; blue circles represent ancestors of outcome variables; blue circles with a line represent outcome variables; green circles with a triangle represent exposures. Cerebral oxygenation (rSO2); acute kidney injury (AKI); kidney replacement therapy (KRT); adverse events (AEs). Neurocognitive function is defined as performance on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and Kinarm tasks.

Figure 2. Study schema.



Cerebral oxygenation (rSO₂); kidney replacement therapy (KRT); continuous KRT (CKRT); intermittent hemodialysis (iHD); Clinical Frailty Scale (CFS); Clinical Dementia Rating Scale (CDRS); Acute Physiological Assessment and Chronic Health Evaluation (APACHE II); Confusion Assessment Method-ICU-7 (CAM-ICU-7); Repeatable Battery for the Assessment of Neuropsychological Status (RBANS); Medication Adherence Rating Scale (MARS); Manchester Driver Behaviour Questionnaire (MDBQ).

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

			Page
Reporting Item			Number
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	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	24
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 24

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	N/A
Roles and responsibilities: sponsor and funder	#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	N/A
Roles and responsibilities: committees	#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)	N/A
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	6-11
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	N/A
Objectives	#7	Specific objectives or hypotheses	11-12
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, non-inferiority, exploratory)	
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	12-13

1	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)	13
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6	Interventions:	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	14-18
7	description			
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10	Interventions:	#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)	14
11	modifications			
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17	Interventions:	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	14
18	adherence			
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22	Interventions:	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
23	concomitant care			
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26	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	15-18
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37	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)	13-18; Figure 2
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43	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	18
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48	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	13, 18
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52	Methods:			
53	Assignment of			
54	interventions (for			
55	controlled trials)			
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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; not a controlled trial
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; not a controlled trial
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A; not a controlled trial
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A; not a controlled trial
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A; not a controlled trial
Methods: Data collection, management, and analysis			
Data collection plan	#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	14-15
Data collection plan: retention	#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	16, 18

1	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	18-19
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9	Statistics: outcomes	#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	19-21
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14	Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	21
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18	Statistics: analysis population and missing data	#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)	N/A
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24	Methods: Monitoring			
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26	Data monitoring: formal committee	#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
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36	Data monitoring: interim analysis	#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
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41	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	N/A
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46	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
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52	Ethics and dissemination			
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56	Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	21
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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)	13-14
Consent or assent: ancillary studies	#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	18-19
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	24
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18-19
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: trial results	#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	22
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	N/A

1	Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of	N/A
2			biological specimens for genetic or molecular analysis in the	
3			current trial and for future use in ancillary studies, if	
4			applicable	
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8	None The SPIRIT checklist is distributed under the terms of the Creative Commons Attribution License CC-			
9	BY-ND 3.0. This checklist can be completed online using https://www.goodreports.org/ , a tool made by the			
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