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A study protocol for an observational cohort investigating COGnitive outcomes and WELLness in survivors of critical illness: the COGWELL study

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ABSTRACT

Introduction: As survival rates from critical illness improve, strategies to return patients to their baseline cognitive and functional status are important research priorities. Upwards of 9 out of 10 ICU survivors will suffer some degree of cognitive impairment at hospital discharge and approximately half will have decrements that persist for years. While the mechanisms for this newly acquired brain injury are poorly understood, several risk factors have been identified. Unfortunately, it is unclear how to accurately predict long-term cognitive impairment. The purpose of this study is to comprehensively describe the prevalence of sleep abnormalities and their association with cognitive impairment, examine a well-known genetic risk factor for dementia (APOE ε4) that may allow for genetic risk stratification of ICU survivors at greatest risk of cognitive impairment, and determine if EEG is an independent predictor of long-term cognitive impairment, and possibly a candidate intermediate end point for future clinical trials.

Methods and Analysis: This is a multisite, prospective, observational cohort study. The setting for this trial will be medical and surgical intensive care units of five large tertiary care referral centres. The participants will be adult patients admitted to a study ICU and invasively ventilated for ≥3 days who survive to hospital discharge. Participants will undergo follow-up within 7 days of ICU discharge, 6-months, and 1-year. At each time point patients will have an EEG, bloodwork (biomarkers; gene studies), sleep study (actigraphy), complete a number of questionnaires, as well as undergo neuropsychological testing. Measures of sleep efficiency (actigraphy, Richards-Campbell Sleep Questionnaire), sleep fragmentation (actigraphy), circadian rhythmicity (actigraphy), APOE (genotyping); EEG (spectral analysis; connectivity); and biomarkers (levels of selected proinflammatory and anti-inflammatory markers in ρg/mL) will be made. The primary outcome of this study will be long-term cognitive function at 12-months follow-up as measured by the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and Trails Making Tests A and B.

Ethics and Dissemination: The study has received the following approvals: University Health Network Research Ethics Committee (13-6425-BE), Sunnybrook Health Centre Research Ethics Committee (365-2013), Mount Sinai Research Ethics Committee (14-0194-E), and St. Michael's Hospital Research Ethics Committee (14-295). Using traditional and innovative methods, the results will be made available to critical care survivors, their caregivers, the funders, the critical care societies, and other researchers. This study is registered with ClinicalTrials.gov (NCT02086877).

STRENGTHS AND WEAKNESSES

- COGWELL will provide the first multisite, comprehensive study to link sleep and circadian function, rhythmic cortical electrophysiological activity measured by quantitative EEG, and long-term cognitive impairment in survivors of critical illness.
- Our longitudinal study design will allow us to look at changes over time in the same patient, defining the temporal sequence of changes, and providing stronger evidence for causality.
- Based on strong scientific reasoning from other patient populations, if true our genomic association theory would provide an easy way of identifying susceptible individuals who may benefit most from intervention strategies.
- The primary limitation of this study is loss to follow-up and missing data points that would challenge the internal validity of reported results from COGWELL.

BACKGROUND

Context

Cognitive outcomes have been evaluated in various ICU patient populations; mixed critically ill patients who required prolonged mechanical ventilation[1, 2], survivors of sepsis and septic shock[3, 4] and medical patients who underwent elective surgery[5]. Impaired cognition was seen in several domains at varying time periods. Cognitive impairment was seen in 39-91% of patients at hospital discharge, 13-79% at 3 to 6 months follow-up and 20-71% at 1 year[6]. Little is known regarding the interactions between identifiable risk factors (host factors and acute events in the ICU and after ICU discharge), and cognitive function after critical illness. Moreover, there are few objective tools with which to risk stratify patients with regard to persistent cognitive dysfunction. It is only by identifying objective risk factors and risk markers is a first step towards developing and effectively targeting interventions to prevent post-ICU cognitive impairment.

Current Knowledge

Sleep disorders

There is considerable evidence linking sleep disordered breathing and poor sleep quality with cognitive impairment in a variety of patient populations[7-11]. Cognitive domains particularly associated with sleep disruption include working memory, semantic memory, processing speed, and visuospatial abilities[8]. Experimental studies support a number of potential neurobiological mechanisms including accumulation of beta amyloid pathology[12, 13], abnormalities of tau[7], synaptic abnormalities[14], changes in hippocampal long term potentiation[15], impaired hippocampal neurogenesis[16, 17], and gene expression changes[18]. The appeal of sleep and circadian dysfunction as potential mechanisms mediating post-ICU cognitive impairment is that effective interventions exist to improve sleep and circadian function.

Few studies have rigorously evaluated the prevalence of sleep disruption after critical illness, and its potential role in potentiating cognitive impairment. A prospective multicenter cohort study (n=1625), reported no change in self-reported sleep quality in the year following critical illness using a non-validated single instrument assessment[19]. However, subjective reports of sleep quality can be confounded by poor recall and misperception. A second small case series reported sleep disruption and poor sleep efficiency as measured by polysomnography in five out of seven survivors of ARDS each of whom reported sleep difficulties 6 months after hospital discharge[20]. Neither study reported cognitive outcomes. A study demonstrating the prevalence of sleep abnormalities after critical illness

and their longitudinal association with cognitive impairment would yield potential targets for therapy and novel endpoints for ICU based studies.

Proteomics and Genomics

The APOE ε4 allele is a well-established and common genetic risk factor for Alzheimer disease[21-23], and is also a risk factor for cognitive impairment in a number of medical conditions including sleep apnea[11, 24, 25] and following repeated head trauma[26]. Recently, in a longitudinal cohort of 737 community dwelling older adults without dementia, the *APOE* ε4 allele was shown to accentuate the impact of sleep fragmentation on the risk of incident Alzheimer's disease in older persons, an effect that was mediated by the accumulation of tau pathology[7, 27]. In individuals with high sleep fragmentation, the presence of at least one *APOE* ε4 allele (*APOE* ε4 +/- or +/+) was associated with a three times faster rate of cognitive decline as compared to individuals not carrying an APOE ε4 allele (*APOE* ε4 -/-)[7].

Although there are no large studies of genetic susceptibility to cognitive impairment following critical illness, data suggest the APOE ε4 allele can have dramatic effects on the acute cognitive status of critically ill patients. In one study, the APOE ε4 allele was associated with a seven-fold increase in the odds of a long duration of delirium (OR 7.3; 95% CI, 1.8 – 30)[28]. The presence of APOE ε4 was found to have a stronger association with duration of delirium than age, severity of illness score (APACHE II), sepsis or benzodiazepine use[28]. Although the duration of delirium is associated with worse cognitive performance after the ICU, the specific role of the APOE ε4 genotype in this association is unknown. Recent work in non-critically ill elderly patients found that administration of benzodiazepines in healthy elderly subjects (n=42) with the APOE ε4 allele was associated with more pronounced cognitive impairment and slower to recover cognitive functioning[29, 30]. This association was found to be independent of deranged pharmacokinetics. Thus, the possibility arises that APOE ε4 may herald a more pronounced vulnerability to a number of brain insults, including drug-related brain toxicity.

This study may identify *APOE* genotype as a biological marker of susceptibility to cognitive impairment and the disruptive effects on sleep following ICU discharge. If this is true, then *APOE* ε4 positive individuals may represent a subpopulation of critical illness survivors who may benefit form particularly close cognitive monitoring and early intervention to improve sleep and circadian function.

Neurophysiology

Studies have so far been unable to identify patients at higher risk of long-term cognitive impairment using screening tools at hospital discharge. For example, in a study by Woon and colleagues, neither the Folstein Mini Mental Status Examination (MMSE) or MiniCog performance at hospital discharge predicted cognitive impairment at 6-month follow-up[31]. Performance on more sensitive tests of cognitive impairment may have predictive value, but these have not been evaluated. This lack of predictive ability restricts the capacity of clinicians and researchers to adequately risk stratify patients with regard to the likelihood of cognitive impairment.

One candidate predictor for cognitive impairment is quantitative EEG. Serial quantitative EEG has been used to diagnose delirium in older patients (n=25) with and without underlying dementia on an inpatient geriatric psychiatry service[32]. Not only did quantitative EEG (amount of slow wave activity in theta and delta frequencies) prove sensitive, as compared to the clinical exam, for the diagnosis of delirium across a range of underlying etiologies (medication intoxication, hypoxia, and electrolyte disturbances, etc.), it also measured severity of delirium. In the ICU, quantitative EEG has also been found to be a sensitive predictor of mortality in patients with severe sepsis, with well-defined categories (numerical and qualitative variables: no encephalopathic changes, mild encephalopathy and severe encephalopathy) of progressively slower EEG waveforms associated with an increased risk of death, with the highest risk associated with burst suppression[33, 34]. Similar findings were found in a prospective observational study in medical ICU patients, where burst suppression was found to be an independent predictor of death at 6 months[35]. Finally, a recent case series of sepsis survivors showed EEG to be a possible candidate predictor of cognitive impairment. Deficits in verbal learning and memory were associated with low-frequency activity on routine EEG at 6 to 24 months following hospital discharge (indicative of nonspecific brain dysfunction)[4]. This study is supportive of our study hypothesis but is insufficient to answer the question of whether EEG could be used as a predictive tool in studying cognitive function after critical illness as it was limited by small sample size (n=25) and inadequate control of time, as follow-up was not standardized (single data collection point per patient; range of 6-24 months)[4].

Although it is likely an imperfect tool, EEG may be able to provide prognostic information. If quantitative EEG is linked with long-term cognitive outcomes, it may serve as a good intermediate

endpoint in therapeutic trials assessing interventions to decrease the risk of post-ICU cognitive impairment.

Study Aims

Research hypothesis and aims

We hypothesize that critical illness will be associated with decrements in sleep and circadian function, quantifiable by actigraphy, that are in turn associated with worse cognitive performance in ICU survivors at 6 and 12 months after hospital discharge. Second, APOE genotype will be a risk factor for cognitive impairment following a number of brain insults (e.g. intermittent hypoxia, head injury, sleep disruption) and may modify the effect of sleep fragmentation on cognition in ICU survivors. APOE genotype may help predict the trajectory of recovery from critical illness, specifically with respect to cognitive impairment. Finally, we hypothesize that survivors of critical illness with cognitive dysfunction will have a greater proportion of low frequency vs. high frequency cortical electrophysiological activity compared to survivors without cognitive dysfunction. EEG will be a predictor of long-term cognitive impairment and therefore could serve as a surrogate endpoint for clinical trials.

To test our first hypothesis, we will determine the impact of sleep and circadian disruption on long-term cognitive impairment in survivors of critical illness. Further, we will determine the relationship between Apolipoprotein E (*APOE*) genotype, sleep disruption and cognitive impairment in a cohort of survivors of critical illness. This is an exploratory aim to examine for direct associations between *APOE* genotype and cognitive function, as well as for gene and environment interaction (e.g. *APOE* and sleep fragmentation interaction) effects on cognitive function. Lastly, we will determine the relationship between rhythmic cortical electrophysiological activity, measured by serial quantitative electroencephalography (EEG), and long-term cognitive outcomes in a cohort of patients who have survived critical illness and are clinically stable prior to hospital discharge.

METHODS AND ANALYSIS

Study protocol

This is a multisite, prospective, observational cohort study involving five teaching hospitals (Toronto Western Hospital, Toronto General Hospital, St. Michael's Hospital, Mount Sinai Hospital, and Sunnybrook Health Sciences Centre) at the University of Toronto. Study patients will enter the cohort after they have been mechanically ventilated for at least 3 days, after they meet inclusion/exclusion

criteria (see Table 1), and they have survived to ICU discharge. Trained research personnel will obtain informed consent from the patient or their next of kin. Patients will leave the cohort one year after discharge from ICU or at the time of death.

At the time of enrollment, we will record the following data: baseline demographic, admission diagnosis and dates, severity of illness (APACHEII); burden of comorbid illness using Charlson[36] and Elixhauser[37] comorbidities scores; pre-existing cognitive impairment by Informant Questionnaire on Cognitive Decline in the Elderly Short Form (IQCODE-SF); baseline functional status using Katz's Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL) Scale; intensive care unit (ICU) and hospital length of stay (LOS).

Study personnel blinded to study hypothesis will prospectively collect data on important confounders such as hemodynamic and ventilator parameters, glycemic control and the presence or absence of delirium on a daily basis. At the time of study enrollment, information collected on each patient will include the following: APACHE II disease category, patient demographics, dates of hospital and ICU admission, initial date of mechanical ventilation, admission diagnosis, history of comorbid disease(s) present at the time of ICU admission captured by the Charlson and Elixhauser Comorbidity Scales and preexisting dementia by the IQCODE-SF. During the course of each patient's stay in the ICU data will be collected on: acute lung injury score (LIS), Sequential Organ Failure Assessment Score (SOFA), and APACHE II score; mean partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2), central venous pressure, mean arterial pressure and blood glucose, daily mean Riker's sedation agitation score, Confusion Assessment Method in the ICU (CAM-ICU) status and average daily doses of the following medications: benzodiazepines, propofol, narcotics, and dexmedetomidine. All patients will undergo standardized follow-up prior to hospital discharge, and at 6- and 12-months. Outcome variables will be collected at each time point. A trained assessor blinded to our study hypothesis will perform all cognitive assessments. Study participants will be identified with a study number only. No identifying information will be transferred outside of the participating hospital site.

Measurement of Exposures and Confounders

Actigraphy:

Actigraphy is the continuous measurement of an individual's movement using a wristwatch-like device (Actiwatch Spectrum, Phillips Respironics, Bend, OR) and is an objective method of quantifying sleep

and circadian rhythms. It has been validated against polysomnography for the measurement of total sleep time and sleep fragmentation[7, 38] and validated against biochemical markers for the assessment of circadian rhythmicity[39]. All patients will have an actigraph placed on their nondominant wrist days within 1 week of ICU discharge. Recordings will continue while on the inpatient ward; however, the number of days of actigraphic data recorded in hospital is likely to vary depending on severity of illness and trajectory of recovery. If patients are discharged home or to a rehabilitation facility prior to attaining 10 days of actigraphic data, the patient will be asked to continue the recording and return the actigraph to the study centre by pre-paid courier. Patients will return to follow-up clinic at 6- and 12-months where actigraphs will be worn again for 10 days as an outpatient.

All actigraph data will be analyzed using MATLAB (Mathworks, Natick, MA). Markers of sleep and circadian function will include: (1) circadian timing (average time of the activity acrophase [midpoint of 8 consecutive hours] of each 24 hours of greatest activity), (2) sleep duration (determined by the Cole-Kripke algorithm), (3) sleep fragmentation (quantified by K_{RA})[7, 8, 40], and (4) regularity of circadian rhythmicity (determined using the chi-square periodogram)[41].

Richards-Campbell Sleep Questionnaire (RQSQ):

This is a five-item, visual analogue scale designed to assess the perception of sleep in critically ill patients[42]. The scale evaluates perceptions of depth of sleep, sleep onset latency, number of awakenings, time spent awake, and overall sleep quality.

Pittsburgh Sleep Quality Index:

The Pittsburgh Sleep Quality Index (PSQI) is a self-rated questionnaire, assessing sleep quality over a 1-month time interval. Nineteen individual items generate seven "component" scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The sum of scores for these seven components yields one global score; a global PSQI score greater than 5 yielded a diagnostic sensitivity of 89.6% and specificity of 86.5% in distinguishing good and poor sleep quality[43].

Genomics [APOE]:

The APOE coding single-nucleotide polymorphism (SNP) sites rs7412 and rs429358 will be determined using the Invitrogen Snapshot assay at The Centre for Applied Genomics at The Hospital for Sick Children Hospital (Toronto, ON; www.tcag.ca). Blood samples (5-10 ml) will be drawn prior

to discharge in a lavender top ethylenediaminetetraacetic acid tube. Blood will be stored at -20°C prior to being shipped for testing at The Hospital for Sick Children Hospital.

EEG:

Within 7 days after ICU discharge, approximately 30 minutes of EEG activity will be digitally acquired (XLTEK, Oakville, ON) with electrodes placed according to the international 10–20 system with additional surface sphenoidal electrodes. In outpatient follow-up, at 6- and 12-months, 30 minutes of EEG activity will be recorded. Data sampling will occur at a rate of 256 Hz. Power spectra will be calculated for consecutive 4-s windows for each electrode contact, and absolute spectral band power for conventional EEG frequency bands (δ: 0.5–4 Hz; θ: 4–8 Hz; α: 8–13 Hz; β: 13–20 Hz; γ: 20–40 Hz) will be averaged across different windows. Given that global changes are expected, the band power values will be averaged over all electrode contacts. Similar measures have been previously used to characterize Alzheimer's disease and depression and, in the former, were correlated with clinical measures of severity of dementia[44-46].

Beck's Depression Inventory (BDI-II):

This instrument screens for depression using criteria consistent with the Diagnostic and Statistical Manual of Mental Disorders- Fourth Edition. Higher scores (range, 0-63) indicate more depressive symptoms. Based on testing in psychiatric outpatients, depression symptom severity is classified as minimal (score, 0-13), mild (score, 14-19), moderate (score, 20-28), and severe (score, 29-63)[47].

The Informant Questionnaire on Cognitive Decline in the Elderly Short Form (IQCODE-SF):

The IQCODE-SF is a brief questionnaire that uses information provided by an informant (typically a close relative) to assess a person's change in cognitive functioning over the preceding ten years. The questionnaire is often used as a screening test to detect dementia. The standard method used to generate the test score is to take the average rating across 16 situations. A person who has no cognitive decline will have an average score of 3, while scores of greater than 3 indicate that some decline has occurred[48].

Measurement of Outcomes: Long-Term Cognitive Morbidity

Repeatable Battery for the Assessment of Neuropsychological Status (RBANS):

The RBANS is a comprehensive and validated neuropsychometric battery for the evaluation of global cognition, including individual domains of immediate and delayed memory, attention, visuospatial

construction, and language[49]. The population age-adjusted mean (± SD) for the RBANS global cognition score and for the individual domains is 100 ± 15 (on a scale ranging from 40 to 160, with lower scores indicating worse performance).

Trailing Making Tests A and B:

Executive function (specifically, cognitive flexibility) will be tested using the Trail Making tests A and B; age-, sex-, and education-adjusted mean T score is 50 (range 0 to 100), with lower score indicating poor performance[50].

Statistical Analysis Plan

Assessing the epidemiology of long-term cognitive impairment will focus on prevalence, severity and natural history. Prevalence will be determined based on binary assessment of patient having or not having clinically significant cognitive impairment, defined as test scores 1.5 standard deviations (SD) below the population mean. We will screen the covariates using the univariate association between the outcome and level of education, RQSQ and PSQI scores, BDI-II, hospital LOS, and days of mechanical ventilation and selecting those with $p<0.2$. Logistic regression analysis models will be used to determine the association between sleep fragmentation and cognitive impairment at 1-year while adjusting for the variables selected. We will enter into the model only those covariates that are not multicollinear based on the variance inflation factor criterion. Given that we predict we will have approximately 30 events at the 1-year follow-up, this will give us at least 5 events per variable[51].

Generalized estimating equations (GEE) models, to take into account the correlation between the 3 measurements per subject, will be used to determine the association of EEG and the effect of time on cognitive impairment. We will test the association between APOE ε4(+/- or +/+) versus APOE ε4(-/-) and cognitive impairment using χ^2 test. The degree of association between APOE and sleep efficiency will be determined using Spearman's correlation; this information will be used to inform future trials.

We calculated our sample size based on logistic regression analysis with outcome cognitive impairment at 12 months. We used a proportion of 30% cognitive impairment at 1-year in this patient population. We do not know a priori the association between our sleep efficiency variable and the other covariates so we will use a range of R-squared (R-squared obtained by regressing the sleep efficiency variable on the other covariates) from low to moderate (0.1 to 0.5). With a sample size of

approximately 110, we have 80% power with α=0.05 for R-squared=0.5 to detect an absolute increase in percentage of cognitive impairment of 20% (from 30% to 50%) for a decrease in sleep efficiency value with one standard deviation from the mean or an increase of 15% (from 30 to 45%) for a R-squared=0.2. With 110 patients, approximately 20% in the APOE ε4(+/- or +/+) group, a χ^2 test at α=0.05 will be able to detect a 37.5% difference (25% in the APOE ε4[-/-] group and 62.5% in the APOE ε4[+/- or +/+] group) in the cognitive impairment group with about 92% power or about 80% power to detect a difference of 31% (25% in the APOE ε4[-/-] group versus 56% in the APOE ε4[+/- or +/+] group).

A total of approximately 150 patients will be consented to participate. This estimate is based on a calculated 1-year mortality rate of 15% in patients discharged from critical care units and a conservative loss to follow-up rate of 15%.

Methodological Issues

Our longitudinal study design, in which parallel covariates are reliably and repeatedly measured over time, will allow us to look at changes over time in the same patient, defining the temporal sequence of changes, and providing stronger evidence for causality than could be obtained from a cross-sectional design. Although our genomic association theory is an exploratory aim, it is based on strong scientific reasoning from other patient populations and if our hypothesis is true, would provide an easy way of identifying susceptible individuals who may benefit the most from interventions to decrease the risk of cognitive impairment.

The primary limitation of this study is loss to follow-up and missing data points that would challenge the internal validity of reported results from COGWELL. However, our research team has extensive experience in achieving high follow-up rates in similar studies of cognitive function and long-term follow-up of critically ill patients[52-56]. Efforts to minimize loss to follow-up will include respecting the time commitment of patients, formal tracking procedures of patients enrolled including acquiring of multiple contacts for arranging follow-up, strong interpersonal skills of study personnel, and flexible hours for testing[57].

Data Management and Oversight

Site investigators will take responsibility for the conduct of COGWELL. Site investigators will

supervise the day-to-day operation of the project, and are responsible for ensuring that International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines are followed.

Members of the COGWELL research team from the University Health Network will monitor the data. Members will review the first three completed charts from each site as well as a random sample of 10% of completed data thereafter. Monitoring will ensure protocol compliance, proper study management, and timely completion of study procedures.

Data Sharing

The final trial dataset will be available to study investigators, Steering Committee members and the Research Ethic Boards at all participating sites.

ETHICS AND DISSEMINATION

The study has received the following approvals: University Health Network Research Ethics Committee (13-6425-BE), Sunnybrook Health Centre Research Ethics Committee (365-2013), Mount Sinai Research Ethics Committee (14-0194-E), and St. Michael's Hospital Research Ethics Committee (14-295). Using traditional and innovative methods, the results will be made available to critical care survivors, their caregivers, the funders, the critical care societies, and other researchers.

Protocol and Registration

This study is registered with ClinicalTrials.gov (NCT02086877).

Patient Anonymity

A unique study number will identify study participants. Identity of the study participant will be recorded and secured in a locked office with access limited to study personnel. The study data will be anonymized at the time of collection. The data collection form will be destroyed at the end of the study once the data has been published. The principal investigator will destroy the study enrollment log once all results have been verified and published (a minimum of 5 years).

Data storage and security

Data will be stored on institutional network drives with firewalls and security measures in place. Hard copy records will be stored in a locked cabinet in a secure location. Access to records and data will

be limited to study personnel. Study data will be de-identified and a master linking log with identifiers will be kept and stored separately from the data.

Contributions

The study concept and design was conceived by MEW, ASL, MPM, RAW, SEB and GDR. KDW, MST, JOF and MEW will conduct screening and data collection. Analysis will be performed by RLP. MEW prepared the first draft of the manuscript. All authors provided edits and critiqued the manuscript for intellectual content.

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Competing Interests

None declared.

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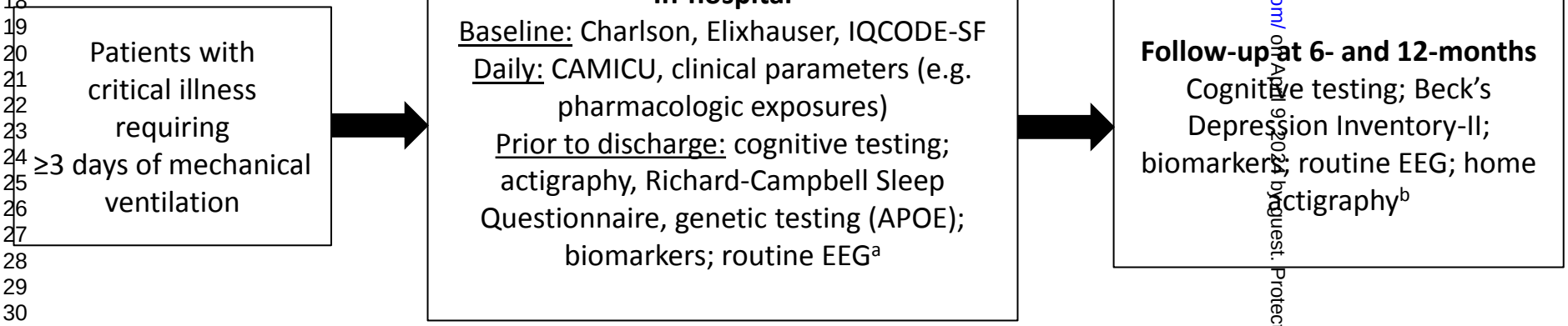
Table 1. Inclusion and Exclusion Criteria

Inclusion criteria	• ≥16 years of age • Admission to study ICU for invasive mechanical ventilation [≥ 3 days]
Exclusion criteria	• Advanced cognitive impairment or unable to follow simple commands before their acute illness [e.g. end-stage Alzheimer's disease] • Primary neurological injury [e.g. anoxic injury, stroke or traumatic brain injury] • Anticipated death within 3 months of discharge [e.g. palliative] • Uncontrolled psychiatric illness at hospital admission • Not fluent in English • Unlikely to adhere with follow-up [e.g. no fixed address] • Residence greater than 300 kms from referral centre

Figure 1. Flow diagram of the Cognitive Outcome and Wellness in survivors of critical illness (COGWELL) study.



[a] 30-mins of routine EEG activity; first 18 patients had 12-16 hours of overnight recording.
[b] 10 days of home actigraphy; set-up will be explained at follow-up appointment.

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

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym **(p. 1)**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry **(p. 3 and 14)**
	2b	All items from the World Health Organization Trial Registration Data Set **(N/A)**
Protocol version	3	Date and version identifier **(N/A)**
Funding	4	Sources and types of financial, material, and other support **(p. 15)**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors **(p. 1 and 15)**
	5b	Name and contact information for the trial sponsor **(N/A)**
	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)**
	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) **(p. 13-14)**
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 **(p. 5-7)**
	6b	Explanation for choice of comparators **(N/A)**
Objectives	7	Specific objectives or hypotheses **(p. 8)**

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) **(p. 8)**
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 **(p. 8)**
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) **(p. 19)**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered **(N/A)**
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) **(N/A)**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) **(N/A)**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial **(N/A)**
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended **(p. 9-11)**
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) **(Figure 1)**
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 **(p. 12-13)**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size **(p. 13)**
Methods: Assignment of interventions (for controlled trials)		
Allocation:		

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions **(N/A)**
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned **(N/A)**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions **(N/A)**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how **(N/A)**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial **(N/A)**
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol **(p. 9)**
	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 **(p. 13)**
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 **(p. 13-14)**
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol **(p. 12-13)**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) **(N/A)**
	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	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed **(N/A)**
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial **(N/A)**
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct **(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 **(p. 14)**
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) **(p. 9)**
	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 **(p. 14)**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site **(p. 15)**
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators **(p. 14)**
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation **(N/A)**

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions **(p. 14)**
	31b	Authorship eligibility guidelines and any intended use of professional writers **(N/A)**
	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 **(Appendix)**
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable **(N/A)**

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

UHN Toronto General Toronto Western Princess Margaret Toronto Rehab
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CONSENT TO PARTICIPATE IN A RESEARCH STUDY

STUDY TITLE: COGWELL: COGnitive outcomes and WELLness in survivors of critical illness

PRINCIPAL INVESTIGATOR (Study Doctor): **Dr. M. Elizabeth Wilcox**
Toronto Western Hospital
Telephone: 416-603-5800 ext. 6203

24-HOUR PHONE NUMBER: **Toronto Western Hospital ICU**
Telephone: 416-603-5818
(Ask for the attending physician on call)

This consent is directed to the patient, but, in the event that the patient is unable to give consent on his/her behalf, a next-of-kin or legal representative may provide consent on the patient's behalf.

INTRODUCTION

You are being asked to take part in a research study. Please read this explanation about the study and its risks and benefits before you decide if you would like to take part. You should take as much time as you need to make your decision. You should ask the study doctor or study staff to explain anything that you do not understand and make sure that all of your questions have been answered before signing this consent form. Before you make your decision, feel free to talk about this study with anyone you wish including your friends, family, and family doctor. Participation in this study is voluntary. Regardless of your decision, you will continue to receive the best care possible at the University Health Network.

BACKGROUND/PURPOSE

You are being asked to take part in this study because you have an acute illness that required mechanical ventilation in the intensive care unit (ICU). There is currently very little information available on the long-term outcomes after ICU. Upwards of 9 out of 10 patients may experience problems with their memory and attention, and in approximately half of patients these problems can last for years. Two important questions are 1) whether or not we can predict which patients will have memory or attention problem years later and 2) are there things that can be done to minimize the effect of critical illness on memory and attention?

STUDY DESIGN

The purpose of this study is to learn what the one-year memory, attention and concentration, and day-to-day function (ability to balance check book, make a shopping list, etc.) is in patients who have been on a mechanical ventilator for at least 3 days. We also want to see how sleep quality and different blood changes may affect one-year performance on these tests. Lastly, this study wants to see if a routine test to measure brain activity can predict who will have memory, attention and concentration, and day-to-day function at one-year follow-up.

While in the ICU, you have received standard care. as required by your diagnosis and clinical symptoms. Taking part in the study does not involve changes in the care that you will be receiving while at the University Health Network. If you choose to take part, a set of tests will be done in addition to those routinely done during your hospital stay.

The APOE (Apolipoprotein E) blood test is a test for genetic risk factors for Alzheimer's disease. The sample will be taken to check for the relationship between Apolipoprotein E and sleep disruption and memory, attention, and concentration in survivors of critical illness. This sample will be collected while you are still in hospital and sent to the Hospital for Sick Children, Toronto, ON for analysis. Another blood sample will be tested to see how the activity of the immune system changes over time after critical illness. This sample will be stored at the University Health Network and then tested at the University of Toronto. The results of these tests will not be available to study participants. The blood samples will be destroyed after the testing is done.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 150 patients will be taking part in this study. Of those 150 patients, around 100 will be at the University Health Network.

PROCEDURES

Study visits:

Within the first week after discharge from the ICU, if you are able, you will be asked to:

- Provide a 10-20 ml blood sample for two blood tests: the APOE and biomarkers.
- Wear a wristwatch-like device (actigraph) for 10-days to measure continuously your movement to assess amount and quality of your sleep.
- Stickers will be put on your head to monitor your brain activity during the early evening and overnight (approximately 8-12 hours).
- Complete questionnaires that will ask about quality of sleep in the ICU and memory, attention and concentration after ICU discharge. These questionnaires will take approximately 20 minutes to complete.
- A family member or a close friend will be asked to complete a questionnaire describing how your memory, attention and concentration were prior to being admitted to the hospital. This will take approximately 10 minutes to complete.

You will be seen in clinic at the University Health Network at 6- and 12-months after your discharge from the ICU. You will be contacted 2-3 weeks before your follow-up appointment to confirm availability. As part of these visits, you will be asked to:

- Provide a 10-20 ml blood sample for biomarkers.
- Wear an actigraph for 10 days, after which time you will return it to the study centre by pre-paid courier.
- Each participant will undergo a one-time formal at-home assessment for sleep apnea (monitoring of your breathing patterns during your sleep to see if oxygen levels change).

- Wear stickers on your head to monitor your brain activity for approximately 1 hour.
- Complete questionnaires that will assess your quality of sleep, memory, attention, and concentration, and mood. These will take approximately 10 minutes each to complete.

The entire follow-up appointment should take approximately 2 hours. If preferred, you can have your memory testing done over the phone and the mood questionnaire could be completed at home and mailed. This would decrease your follow-up appointment to less than 90 minutes.

VOLUNTARY PARTICIPATION

The study participant's participation in this study is voluntary. You can choose not to be in the study or you may leave the study at any time without affecting your medical care. Throughout the study, you will be advised of any new information that might affect your decision to remain in the study.

WITHDRAWAL FROM STUDY

If you decide to leave the study, the information that was collected before you leave the study will still be used in order to help answer the research question. No new information will be collected without your permission.

RISKS

This study has risks. Some of these risks we know about. There is also a possibility of risks that we do not know about and have not been seen in study participants to date. Please call the study doctor if you have any side effects even if you do not think it has anything to do with this study. The risks we know of are:

- Blood tests: To reduce and/or minimize any discomfort you may experience, whenever possible, we will take a blood sample while blood is being drawn as part of your standard clinical care. Blood will be taken from either a tube already inserted into your artery or if you do not have this, we will have to take it from a needle inserted into your vein. If the sample is taken using a needle you may experience discomfort or pain, and there may be a small amount of bleeding. You may experience a slight discomfort, bruising, bleeding, swelling or redness at the place of the needle puncture site. There is also a slight chance of infection at the place where the needle punctures your skin.

- The measures of brain activity: During the test to see what happens in the brain, the technician may encourage the patient to do things that stimulate the brain such as deep breathing or flashing lights. As a result, you may feel dizziness or lightheadedness. It is uncommon and will resolve in minutes. Mild irritation can rarely be experienced from the preparation of the skin and cream used to attach the electrodes to the scalp for recordings. This is typically very mild and resolves within hours to days. The glue used to attach electrodes has a bad smell and may cause headaches, irritation of the eyes, rarely a skin reaction. Again, these reactions are usually mild and resolve quickly.

BENEFITS

You may receive no direct benefits from being in this study. However, results from this study may further medical and/or scientific knowledge.

ALTERNATIVES TO BEING IN THE STUDY

If you do not take part in the study, you will be followed up as per clinical care usual schedule.

CONFIDENTIALITY

If you agree to join this study, the study doctor and his/her team will look at your personal health information and collect only the information they need for the study. Personal health information is any information is any information that could identify you and includes your:

- Name,
- Address,
- Date of birth,
- Postal code,
- New or existing medical records that includes types, dates and results of medical tests or procedures.

Only the study team or the people or groups listed below will be allowed to look at your records. Your participation in this study also may be recorded in your medical record at this hospital. This is for clinical safety purposes.

The following people may come to the hospital to look at the study records and at your personal health information to check that the information collected for the study is correct and to make sure the study is following proper laws and guidelines:

- Representatives of the University Health Network (UHN) including the UHN Research Ethics Board

All information obtained during the study will be held in strict confidence. The study participant will be identified with a study number only. No names or identifying information will be used in any publication or presentations. No information identifying you will be transferred outside the investigators in this study or this hospital.

COSTS

You will not have to pay for any of the procedures involved with this study. You will be given 25$ to cover parking for each of the two visits that you make to the hospital for the study.

RIGHTS AS A PARTICIPANT

If you are harmed as a direct result of taking part in this study, all necessary medical treatment will be made available to you at no cost.

By signing this form you do not give up any of your legal rights against the investigators, sponsor or involved institutions for compensation, nor does this form relieve the investigators, sponsor or involved institutions of their legal and professional responsibilities.

CONFLICT OF INTEREST

Researchers have an interest in completing this study. Their interests should not influence your decision to participate in this study.

QUESTIONS ABOUT THE STUDY

If the study participant suffers any side effects or other injuries during the study, or if you have any general questions about the study, please call the doctor in charge of this study, Dr. Elizabeth Wilcox at (416) 603-6203. You may also contact Ms. Paulina Farias (study coordinator, Medical/Surgical ICU) at (416) 603-5967 or Ms. Andrea Matte (study coordinator, Medical/Surgical ICU) at (416) 340-3842, at any time.

If you have any questions about the study participant's rights as a research participant or have concerns about this study, call the Chair of the University Health Network Research Ethics Board (REB) or the Research Ethics office number at 416-581-7849. The REB is a group of people who oversee the ethical conduct of research studies. These people are not part of the study team. Everything that you discuss will be kept confidential.

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DOCUMENTATION OF INFORMED CONSENT

Study Title: **COGWELL:** COGnitive Outcomes and WELLness in Survivors of Critical Illness

This study has been explained to me and any questions I had have been answered.
I know that I may leave the study at any time. I agree to take part in this study.

_____	_____	_____
Print Study Participant's Name	Signature	Date

(You will be given a signed copy of this consent form)

My signature means that I have explained the study to the participant named above. I have answered all questions.

_____	_____	_____
Name of participant (print)	Signature	Date

_____	_____	_____
Substitute decision-maker (print)	Signature	Date

_____	_____	_____
Name of Person obtaining consent (print)	Signature	Date

BMJ Open

A study protocol for an observational cohort investigating COGnitive outcomes and WELLness in survivors of critical illness: the COGWELL study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-015600.R1
Article Type:	Protocol
Date Submitted by the Author:	31-Mar-2017
Complete List of Authors:	Wilcox, M. Elizabeth; University of Toronto, Interdepartmental Division of Critical Care; University Health Network Lim, Andrew; Sunnybrook Health Sciences Centre McAndrews, Mary; University Health Network; Krembil Wennberg, Richard; University Health Network Pinto, Ruxandra; Sunnybrook Health Sciences Centre Black, Sandra; Sunnybrook Health Sciences Centre, Neurology Walczak, Karolina; University Health Network Friedrich, Jan; University of Toronto, Interdepartmental Division of Critical Care; St. Michael's Hospital, Department of Medicine Taglione, Michael; University of Toronto Faculty of Medicine, ; St. Michael's Hospital, Li Ka Shing Knowledge Institute Rubenfeld, Gordon; Universityof Toronto, Critical Care; Sunnybrook Health Sciences Centre
Primary Subject Heading:	Health services research
Secondary Subject Heading:	Respiratory medicine
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A study protocol for an observational cohort investigating COGnitive outcomes and WELLness in survivors of critical illness: the COGWELL study

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ABSTRACT

Introduction: As survival rates from critical illness improve, strategies to return patients to their baseline cognitive and functional status are important research priorities. Upwards of 9 out of 10 ICU survivors will suffer some degree of cognitive impairment at hospital discharge and approximately half will have decrements that persist for years. While the mechanisms for this newly acquired brain injury are poorly understood, several risk factors have been identified. Unfortunately, it is unclear how to accurately predict long-term cognitive impairment. The purpose of this study is to comprehensively describe the prevalence of sleep abnormalities and their association with cognitive impairment, examine a well-known genetic risk factor for dementia (APOE ε4) that may allow for genetic risk stratification of ICU survivors at greatest risk of cognitive impairment, and determine if EEG is an independent predictor of long-term cognitive impairment, and possibly a candidate intermediate end point for future clinical trials.

Methods and Analysis: This is a multisite, prospective, observational cohort study. The setting for this trial will be medical and surgical intensive care units of five large tertiary care referral centres. The participants will be adult patients admitted to a study ICU and invasively ventilated for ≥3 days who survive to hospital discharge. Participants will undergo follow-up within 7 days of ICU discharge, 6-months, and 1-year. At each time point patients will have an EEG, blood work (biomarkers; gene studies), sleep study (actigraphy), complete a number of questionnaires, as well as undergo neuropsychological testing. Measures of sleep efficiency (actigraphy, Richards-Campbell Sleep Questionnaire), sleep fragmentation (actigraphy), circadian rhythmicity (actigraphy), APOE (genotyping); EEG (spectral analysis; connectivity); and biomarkers (levels of selected pro-inflammatory and anti-inflammatory markers in ρg/mL) will be made. The primary outcome of this study will be long-term cognitive function at 12-months follow-up as measured by the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and Trails Making Tests A and B.

Ethics and Dissemination: The study has received the following approvals: University Health Network Research Ethics Committee (13-6425-BE), Sunnybrook Health Centre Research Ethics Committee (365-2013), Mount Sinai Research Ethics Committee (14-0194-E), and St. Michael's Hospital Research Ethics Committee (14-295). Using traditional and innovative methods, the results will be made available to critical care survivors, their caregivers, the funders, the critical care societies, and other researchers. This study is registered with ClinicalTrials.gov (NCT02086877).

STRENGTHS AND WEAKNESSES

- COGWELL will provide the first multisite, comprehensive study to investigate sleep and circadian function, rhythmic cortical electrophysiological activity measured by quantitative EEG, and long-term cognitive impairment in survivors of critical illness.
- Our longitudinal study design will allow us to look at changes over time in the same patient, defining the temporal sequence of changes, and providing stronger evidence for causality.
- Based on strong scientific reasoning from other patient populations, if true our genomic association theory would provide a way of identifying susceptible individuals who may benefit most from intervention strategies.
- The primary limitation of this study is loss to follow-up and missing data points that would challenge the internal validity of reported results from COGWELL.

BACKGROUND

Context

Cognitive outcomes have been evaluated in various ICU patient populations; mixed critically ill patients who required prolonged mechanical ventilation[1, 2], survivors of sepsis and septic shock[3, 4] and medical patients who underwent elective surgery[5]. Impaired cognition was seen in several domains at varying time periods. Cognitive impairment was seen in 39-91% of patients at hospital discharge, 13-79% at 3 to 6 months follow-up and 20-71% at 1 year[6]. Little is known regarding the interactions between identifiable risk factors (host factors and acute events in the ICU and after ICU discharge), and cognitive function after critical illness. Moreover, there are few objective tools with which to risk stratify patients with regard to persistent cognitive dysfunction. Identifying objective risk factors and risk markers are first steps towards developing and effectively targeting interventions to prevent post-ICU cognitive impairment.

Current Knowledge

Sleep disorders

There is considerable evidence linking sleep disordered breathing and poor sleep quality with cognitive impairment in a variety of patient populations[7-11]. Cognitive domains particularly associated with sleep disruption include working memory, semantic memory, processing speed, and visuospatial abilities[8]. Experimental studies support a number of potential neurobiological mechanisms including accumulation of beta amyloid pathology[12, 13], abnormalities of tau[7], synaptic abnormalities[14], changes in hippocampal long term potentiation[15], impaired hippocampal neurogenesis[16, 17], and gene expression changes[18]. The appeal of sleep and circadian dysfunction as potential mechanisms mediating post-ICU cognitive impairment is that effective interventions exist to improve sleep and circadian function.

Few studies have rigorously evaluated the prevalence of sleep disruption after critical illness, and its potential role in potentiating cognitive impairment. A prospective multicenter cohort study (n=1625), reported no change in self-reported sleep quality in the year following critical illness using a non-validated single instrument assessment[19]. However, subjective reports of sleep quality can be confounded by poor recall and misperception. A second small case series reported sleep disruption and poor sleep efficiency as measured by polysomnography in five out of seven survivors of ARDS each of whom reported sleep difficulties 6 months after hospital discharge[20]. Neither study reported cognitive outcomes. A study demonstrating the prevalence of sleep abnormalities after critical illness

and their longitudinal association with cognitive impairment would yield potential targets for therapy and novel endpoints for ICU based studies.

Proteomics and Genomics

The Apolipoprotein E (*APOE*) ε4 allele is a well-established and common genetic risk factor for Alzheimer disease[21-23], and is also a risk factor for cognitive impairment in a number of medical conditions including sleep apnea[11, 24, 25] and following repeated head trauma[26]. Recently, in a longitudinal cohort of 737 community dwelling older adults without dementia, the *APOE* ε4 allele was shown to accentuate the impact of sleep fragmentation on the risk of incident Alzheimer's disease in older persons, an effect that was mediated by the accumulation of tau pathology[7, 27]. In individuals with high sleep fragmentation, the presence of at least one *APOE* ε4 allele (*APOE* ε4 +/- or +/+) was associated with a three times faster rate of cognitive decline as compared to individuals not carrying an APOE ε4 allele (*APOE* ε4 -/-)[7].

Although there are no large studies of genetic susceptibility to cognitive impairment following critical illness, data suggest the APOE ε4 allele can have dramatic effects on the acute cognitive status of critically ill patients. In one study, the APOE ε4 allele was associated with a seven-fold increase in the odds of a long duration of delirium (OR 7.3; 95% CI, 1.8 – 30)[28]. The presence of APOE ε4 was found to have a stronger association with duration of delirium than age, severity of illness score (APACHE II), sepsis or benzodiazepine use[28]. Although the duration of delirium is associated with worse cognitive performance after the ICU, the specific role of the APOE ε4 genotype in this association is unknown. Recent work in non-critically ill elderly patients found that administration of benzodiazepines in healthy elderly subjects (n=42) with the APOE ε4 allele was associated with more pronounced cognitive impairment and slower to recover cognitive functioning[29, 30]. This association was found to be independent of deranged pharmacokinetics. Thus, the possibility arises that APOE ε4 may herald a more pronounced vulnerability to a number of brain insults, including drug-related brain toxicity.

This study may identify *APOE* genotype as a biological marker of susceptibility to cognitive impairment and the disruptive effects on sleep following ICU discharge. If this is true, then *APOE* ε4 positive individuals may represent a subpopulation of critical illness survivors who may benefit form particularly close cognitive monitoring and early intervention to improve sleep and circadian function.

Neurophysiology

Studies have so far been unable to identify patients at higher risk of long-term cognitive impairment using screening tools at hospital discharge. For example, in a study by Woon and colleagues, neither the Folstein Mini Mental Status Examination (MMSE) or MiniCog performance at hospital discharge predicted cognitive impairment at 6-month follow-up[31]. Performance on more sensitive tests of cognitive impairment may have predictive value, but these have not been evaluated. This lack of predictive ability restricts the capacity of clinicians and researchers to adequately risk stratify patients with regard to the likelihood of cognitive impairment.

One candidate predictor for cognitive impairment is quantitative electroencephalography (EEG). Serial quantitative EEG has been used to diagnose delirium in older patients (n=25) with and without underlying dementia on an inpatient geriatric psychiatry service[32]. Not only did quantitative EEG (amount of slow wave activity in theta and delta frequencies) prove sensitive, as compared to the clinical exam, for the diagnosis of delirium across a range of underlying etiologies (medication intoxication, hypoxia, and electrolyte disturbances, etc.), it also measured severity of delirium. In the ICU, quantitative EEG has also been found to be a sensitive predictor of mortality in patients with severe sepsis, with well-defined categories (numerical and qualitative variables: no encephalopathic changes, mild encephalopathy and severe encephalopathy) of progressively slower EEG waveforms associated with an increased risk of death, with the highest risk associated with burst suppression[33, 34]. Similar findings were found in a prospective observational study in medical ICU patients, where burst suppression was found to be an independent predictor of death at 6 months[35]. Finally, a recent case series of sepsis survivors showed EEG to be a possible candidate predictor of cognitive impairment. Deficits in verbal learning and memory were associated with low-frequency activity on routine EEG at 6 to 24 months following hospital discharge (indicative of nonspecific brain dysfunction)[4]. This study is supportive of our study hypothesis but is insufficient to answer the question of whether EEG could be used as a predictive tool in studying cognitive function after critical illness as it was limited by small sample size (n=25) and inadequate control of time, as follow-up was not standardized (single data collection point per patient; range of 6-24 months)[4].

Although it is likely an imperfect tool, EEG may be able to provide prognostic information. If quantitative EEG is linked with long-term cognitive outcomes, it may serve as a good intermediate

endpoint in therapeutic trials assessing interventions to decrease the risk of post-ICU cognitive impairment.

Study Aims

Research hypothesis and aims

We hypothesize that critical illness will be associated with decrements in sleep and circadian function, quantifiable by actigraphy, that are in turn associated with worse cognitive performance in ICU survivors at 6 and 12 months after hospital discharge. Second, APOE genotype will be a risk factor for cognitive impairment following a number of brain insults (e.g. intermittent hypoxia, sleep disruption) and may modify the effect of sleep fragmentation on cognition in ICU survivors. APOE genotype may help predict the trajectory of recovery from critical illness, specifically with respect to cognitive impairment. Finally, we hypothesize that survivors of critical illness with cognitive dysfunction will have a greater proportion of low frequency vs. high frequency cortical electrophysiological activity compared to survivors without cognitive dysfunction. EEG will be a predictor of long-term cognitive impairment and therefore could serve as a surrogate endpoint for clinical trials.

To test our first hypothesis, we will determine the impact of sleep and circadian disruption on long-term cognitive impairment in survivors of critical illness. Further, we will determine the relationship between the APOE genotype, sleep disruption and cognitive impairment in a cohort of survivors of critical illness. This is an exploratory aim to examine for direct associations between *APOE* genotype and cognitive function, as well as for gene and environment interaction (e.g. *APOE* and sleep fragmentation interaction) effects on cognitive function. Lastly, we will determine the relationship between rhythmic cortical electrophysiological activity, measured by serial quantitative EEG, and long-term cognitive outcomes in a cohort of patients who have survived critical illness and are clinically stable prior to hospital discharge.

METHODS AND ANALYSIS

Study protocol

This is a multisite, prospective, observational cohort study involving five teaching hospitals (Toronto Western Hospital, Toronto General Hospital, St. Michael's Hospital, Mount Sinai Hospital, and Sunnybrook Health Sciences Centre) at the University of Toronto. Study patients will enter the cohort after they have been mechanically ventilated for at least 3 days, after they meet inclusion/exclusion

criteria (see Table 1), and they have survived to ICU discharge. Trained research personnel will obtain informed consent from the patient or their next of kin. Patients will leave the cohort one year after discharge from ICU or at the time of death.

At the time of enrollment, we will record the following data: baseline demographic, admission diagnosis and dates, severity of illness (APACHEII); burden of comorbid illness using Charlson[36] and Elixhauser[37] comorbidities scores; pre-existing cognitive impairment by Informant Questionnaire on Cognitive Decline in the Elderly Short Form (IQCODE-SF); intensive care unit (ICU) and hospital length of stay (LOS).

Study personnel blinded to study hypothesis will prospectively collect data on important confounders such as hemodynamic and ventilator parameters, glycemic control and the presence or absence of delirium on a daily basis. At the time of study enrollment, information collected on each patient will include the following: APACHE II disease category, patient demographics, dates of hospital and ICU admission, initial date of mechanical ventilation, admission diagnosis, history of comorbid disease(s) present at the time of ICU admission captured by the Charlson and Elixhauser Comorbidity Scales and preexisting dementia by the IQCODE-SF. During the course of each patient's stay in the ICU data will be collected on: acute lung injury score (LIS), Sequential Organ Failure Assessment Score (SOFA), and APACHE II score; mean partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2), central venous pressure, mean arterial pressure and blood glucose, daily mean Riker's sedation agitation score, Confusion Assessment Method in the ICU (CAM-ICU) status and average daily doses of the following medications: benzodiazepines, propofol, narcotics, and dexmedetomidine. All patients will undergo standardized follow-up prior to hospital discharge, and at 6- and 12-months. Outcome variables will be collected at each time point. A trained assessor blinded to our study hypothesis will perform all cognitive assessments. Study participants will be identified with a study number only. No identifying information will be transferred outside of the participating hospital site.

Measurement of Exposures and Confounders

Actigraphy:

Actigraphy is the continuous measurement of an individual's movement using a wristwatch-like device (Actiwatch Spectrum, Phillips Respironics, Bend, OR) and is an objective method of quantifying sleep and circadian rhythms. It has been validated against polysomnography for the measurement of total

sleep time and sleep fragmentation[7, 38] and validated against biochemical markers for the assessment of circadian rhythmicity[39]. All patients will have an actigraph placed on their nondominant wrist days within 1 week of ICU discharge. Recordings will continue while on the inpatient ward; however, the number of days of actigraphic data recorded in hospital is likely to vary depending on severity of illness and trajectory of recovery. If patients are discharged home or to a rehabilitation facility prior to attaining 10 days of actigraphic data, the patient will be asked to continue the recording and return the actigraph to the study centre by pre-paid courier. Patients will return to follow-up clinic at 6- and 12-months where actigraphs will be worn again for 10 days as an outpatient.

All actigraph data will be analyzed using MATLAB (Mathworks, Natick, MA). Markers of sleep and circadian function will include: (1) circadian timing (average time of the activity acrophase [midpoint of 8 consecutive hours] of each 24 hours of greatest activity), (2) sleep duration (determined by the Cole-Kripke algorithm), (3) sleep fragmentation (quantified by K_{RA})[7, 8, 40], and (4) regularity of circadian rhythmicity (determined using the chi-square periodogram)[41].

Richards-Campbell Sleep Questionnaire (RCSQ):

This is a five-item, visual analogue scale designed to assess the perception of sleep in critically ill patients[42]. The scale evaluates perceptions of depth of sleep, sleep onset latency, number of awakenings, time spent awake, and overall sleep quality.

Pittsburgh Sleep Quality Index:

The Pittsburgh Sleep Quality Index (PSQI) is a self-rated questionnaire, assessing sleep quality over a 1-month time interval. Nineteen individual items generate seven "component" scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The sum of scores for these seven components yields one global score; a global PSQI score greater than 5 yielded a diagnostic sensitivity of 89.6% and specificity of 86.5% in distinguishing good and poor sleep quality[43].

Genomics [APOE]:

The APOE coding single-nucleotide polymorphism (SNP) sites rs7412 and rs429358 will be determined using the Invitrogen Snapshot assay at The Centre for Applied Genomics at The Hospital for Sick Children Hospital (Toronto, ON; www.tcag.ca). Blood samples (5-10 ml) will be drawn prior

to discharge in a lavender top ethylenediaminetetraacetic acid tube. Blood will be stored at -20°C prior to being shipped for testing at The Hospital for Sick Children Hospital.

EEG:

Within 7 days after ICU discharge, approximately 30 minutes of EEG activity will be digitally acquired (XLTEK, Oakville, ON) with electrodes placed according to the international 10–20 system with additional surface sphenoidal electrodes. In outpatient follow-up, at 6- and 12-months, 30 minutes of EEG activity will be recorded. Data sampling will occur at a rate of 256 Hz. Power spectra will be calculated for consecutive 4-s windows for each electrode contact, and absolute spectral band power for conventional EEG frequency bands (δ: 0.5–4 Hz; θ: 4–8 Hz; α: 8–13 Hz; β: 13–20 Hz; γ: 20–40 Hz) will be averaged across different windows. Given that global changes are expected, the band power values will be averaged over all electrode contacts. Similar measures have been previously used to characterize Alzheimer's disease and depression and, in the former, were correlated with clinical measures of severity of dementia[44-46].

Beck's Depression Inventory (BDI-II):

This instrument screens for depression using criteria consistent with the Diagnostic and Statistical Manual of Mental Disorders- Fourth Edition. Higher scores (range, 0-63) indicate more depressive symptoms. Based on testing in psychiatric outpatients, depression symptom severity is classified as minimal (score, 0-13), mild (score, 14-19), moderate (score, 20-28), and severe (score, 29-63)[47].

The Informant Questionnaire on Cognitive Decline in the Elderly Short Form (IQCODE-SF):

The IQCODE-SF is a brief questionnaire that uses information provided by an informant (typically a close relative) to assess a person's change in cognitive functioning over the preceding ten years. The questionnaire is often used as a screening test to detect dementia. The standard method used to generate the test score is to take the average rating across 16 situations. A person who has no cognitive decline will have an average score of 3, while scores of greater than 3 indicate that some decline has occurred[48].

Measurement of Outcomes: Long-Term Cognitive Morbidity

Repeatable Battery for the Assessment of Neuropsychological Status (RBANS):

The RBANS is a comprehensive and validated neuropsychometric battery for the evaluation of global cognition, including individual domains of immediate and delayed memory, attention, visuospatial

construction, and language[49]. The population age-adjusted mean (± SD) for the RBANS global cognition score and for the individual domains is 100 ± 15 (on a scale ranging from 40 to 160, with lower scores indicating worse performance). The RBANS has been validated in diverse patient populations including those with mild cognitive impairment, moderate to severe traumatic brain injuries, vascular dementias, and Alzheimer's Disease[50-53].

Trailing Making Tests A and B:

Executive function (specifically, cognitive flexibility) will be tested using the Trail Making tests A and B; age-, sex-, and education-adjusted mean T score is 50 (range 0 to 100), with lower score indicating poor performance[54].

Statistical Analysis Plan

Assessing the epidemiology of long-term cognitive impairment will focus on prevalence, severity and natural history. Prevalence will be determined based on binary assessment of patient having or not having clinically significant cognitive impairment, defined as test scores 1 standard deviations (SD) below the population mean on the RBANS global cognition score. We will screen the covariates using the univariate association between the outcome and level of education, RCSQ and PSQI scores, BDI-II, hospital LOS, and days of mechanical ventilation and selecting those with $p<0.2$. Logistic regression analysis models will be used to determine the association between sleep fragmentation and cognitive impairment at 1-year while adjusting for the variables selected. We will enter into the model only those covariates that are not multicollinear based on the variance inflation factor criterion. Given that we predict we will have approximately 30 events at the 1-year follow-up, this will give us at least 5 events per variable[55].

Generalized estimating equations (GEE) models, to take into account the correlation between the 3 measurements per subject, will be used to determine the association of EEG and the effect of time on cognitive impairment. We will test the association between APOE ε4(+/- or +/+) versus APOE ε4(-/-) and cognitive impairment using χ^2 test. The degree of association between APOE and sleep efficiency will be determined using Spearman's correlation; this information will be used to inform future trials.

We calculated our sample size based on logistic regression analysis with outcome cognitive impairment at 12 months. We used a proportion of 30% cognitive impairment at 1-year in this patient

population. We do not know a priori the association between our sleep efficiency variable and the other covariates so we will use a range of R-squared (R-squared obtained by regressing the sleep efficiency variable on the other covariates) from low to moderate (0.1 to 0.5). With a sample size of approximately 110, we have 80% power with α=0.05 for R-squared=0.5 to detect an absolute increase in percentage of cognitive impairment of 20% (from 30% to 50%) for a decrease in sleep efficiency value with one standard deviation from the mean or an increase of 15% (from 30 to 45%) for a R-squared=0.2. With 110 patients, approximately 20% in the APOE ε4(+/- or +/+) group, a χ^2 test at α=0.05 will be able to detect a 37.5% difference (25% in the APOE ε4[-/-] group and 62.5% in the APOE ε4[+/- or +/+] group) in the cognitive impairment group with about 92% power or about 80% power to detect a difference of 31% (25% in the APOE ε4[-/-] group versus 56% in the APOE ε4[+/- or +/+] group).

A total of approximately 150 patients will be consented to participate. This estimate is based on a calculated 1-year mortality rate of 15% in patients discharged from critical care units and a conservative loss to follow-up rate of 15%.

Methodological Issues

Our longitudinal study design, in which parallel covariates are reliably and repeatedly measured over time, will allow us to look at changes over time in the same patient, defining the temporal sequence of changes, and providing stronger evidence for causality than could be obtained from a cross-sectional design. Although our genomic association theory is an exploratory aim, it is based on strong scientific reasoning from other patient populations and if our hypothesis is true, would provide an easy way of identifying susceptible individuals who may benefit the most from interventions to decrease the risk of cognitive impairment.

The primary limitation of this study is loss to follow-up and missing data points that would challenge the internal validity of reported results from COGWELL. However, our research team has extensive experience in achieving high follow-up rates in similar studies of cognitive function and long-term follow-up of critically ill patients[56-60]. Efforts to minimize loss to follow-up will include respecting the time commitment of patients, formal tracking procedures of patients enrolled including acquiring of multiple contacts for arranging follow-up, strong interpersonal skills of study personnel, and flexible hours for testing[61].

Data Management and Oversight

Site investigators will take responsibility for the conduct of COGWELL. Site investigators will supervise the day-to-day operation of the project, and are responsible for ensuring that International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines are followed.

Members of the COGWELL research team from the University Health Network will monitor the data. Members will review the first three completed charts from each site as well as a random sample of 10% of completed data thereafter. Monitoring will ensure protocol compliance, proper study management, and timely completion of study procedures.

Data Sharing

The final trial dataset will be available to study investigators, Steering Committee members and the Research Ethic Boards at all participating sites.

ETHICS AND DISSEMINATION

The study has received the following approvals: University Health Network Research Ethics Committee (13-6425-BE), Sunnybrook Health Centre Research Ethics Committee (365-2013), Mount Sinai Research Ethics Committee (14-0194-E), and St. Michael's Hospital Research Ethics Committee (14-295). Using traditional and innovative methods, the results will be made available to critical care survivors, their caregivers, the funders, the critical care societies, and other researchers.

Protocol and Registration

This study is registered with ClinicalTrials.gov (NCT02086877).

Patient Anonymity

A unique study number will identify study participants. Identity of the study participant will be recorded and secured in a locked office with access limited to study personnel. The study data will be anonymized at the time of collection. The data collection form will be destroyed at the end of the study once the data has been published. The principal investigator will destroy the study enrollment log once all results have been verified and published (a minimum of 5 years).

Data storage and security

Data will be stored on institutional network drives with firewalls and security measures in place. Hard copy records will be stored in a locked cabinet in a secure location. Access to records and data will be limited to study personnel. Study data will be de-identified and a master linking log with identifiers will be kept and stored separately from the data.

Contributions

The study concept and design was conceived by MEW, ASL, MPM, RAW, SEB and GDR. KDW, MST, JOF and MEW will conduct screening and data collection. Analysis will be performed by RLP. MEW prepared the first draft of the manuscript. All authors provided edits and critiqued the manuscript for intellectual content.

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Competing Interests

None declared.

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Table 1. Inclusion and Exclusion Criteria

Inclusion criteria	• ≥16 years of age • Admission to study ICU for invasive mechanical ventilation [≥ 3 days]
Exclusion criteria	• Advanced cognitive impairment or unable to follow simple commands before their acute illness [e.g. end-stage Alzheimer's disease] • Primary neurological injury [e.g. anoxic injury, stroke or traumatic brain injury] • Anticipated death within 3 months of discharge [e.g. palliative] • Uncontrolled psychiatric illness at hospital admission • Not fluent in English • Unlikely to adhere with follow-up [e.g. no fixed address] • Residence greater than 300 kms from referral centre

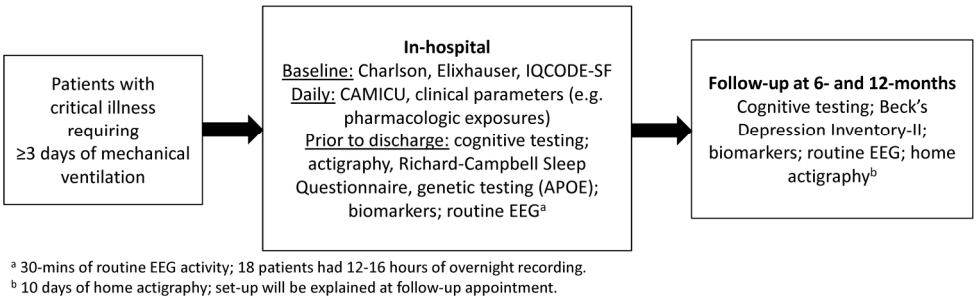

Figure 1. Flow diagram of the Cognitive Outcome and Wellness in survivors of critical illness (COGWELL) study.

190x142mm (300 x 300 DPI)

UHN Toronto General Toronto Western Princess Margaret Toronto Rehab
COURAGE LIVES HERE

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

STUDY TITLE: **COGWELL:** COGnitive outcomes and WELLness in survivors of critical illness

PRINCIPAL INVESTIGATOR (Study Doctor): **Dr. M. Elizabeth Wilcox**
Toronto Western Hospital
Telephone: 416-603-5800 ext. XXXX

24-HOUR PHONE NUMBER: **Toronto Western Hospital ICU**
Telephone: 416-603-XXXX
(Ask for the attending physician on call)

This consent is directed to the patient, but, in the event that the patient is unable to give consent on his/her behalf, a next-of-kin or legal representative may provide consent on the patient's behalf.

INTRODUCTION

You are being asked to take part in a research study. Please read this explanation about the study and its risks and benefits before you decide if you would like to take part. You should take as much time as you need to make your decision. You should ask the study doctor or study staff to explain anything that you do not understand and make sure that all of your questions have been answered before signing this consent form. Before you make your decision, feel free to talk about this study with anyone you wish including your friends, family, and family doctor. Participation in this study is voluntary. Regardless of your decision, you will continue to receive the best care possible at the University Health Network.

BACKGROUND/PURPOSE

You are being asked to take part in this study because you have an acute illness that required mechanical ventilation in the intensive care unit (ICU). There is currently little information available on the long-term outcomes after ICU. Upwards of 9 out of 10 patients may experience problems with their memory and attention, and in approximately half of patients these problems can last for years. Two important questions are 1) whether or not we can predict which patients will have memory or attention problem years later and 2) are there things that can be done to minimize the effect of critical illness on memory and attention?

STUDY DESIGN

The purpose of this study is to learn what the one-year memory, attention and concentration, and day-to-day function (ability to balance check book, make a shopping list, etc.) is in patients who have been on a mechanical ventilator for at least 3 days. We also want to see how sleep quality and different blood changes may affect one-year performance on these tests. Lastly, this study wants to see if a routine test to measure brain activity can predict who will have memory, attention and concentration, and day-to-day function at one-year follow-up.

While in the ICU, you have received standard care as required by your diagnosis and clinical symptoms. Taking part in the study does not involve changes in the care that you will be receiving while at the University Health Network. If you choose to take part, a set of tests will be done in addition to those routinely done during your hospital stay.

The Apolipoprotein E (APOE) blood test is a test for genetic risk factors for Alzheimer's disease. The sample will be taken to check for the relationship between APOE and sleep disruption and memory, attention, and concentration in survivors of critical illness. This sample will be collected while you are still in hospital and sent to the Hospital for Sick Children, Toronto, ON for analysis. Another blood sample will be tested to see how the activity of the immune system changes over time after critical illness. This sample will be stored at the University Health Network and then tested at the University of Toronto. The results of these tests will not be available to study participants. The blood samples will be destroyed after the testing is done.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 150 patients will be taking part in this study. Of those 150 patients, around 100 will be at the University Health Network.

PROCEDURES

Study visits:

Within the first week after discharge from the ICU, if you are able, you will be asked to:

- Provide a 10-20 ml blood sample for two blood tests: the APOE and biomarkers.
- Wear a wristwatch-like device (actigraph) for 10-days to measure continuously your movement to assess amount and quality of your sleep.
- Stickers will be put on your head to monitor your brain activity during the day or early evening (approximately 1 hour).
- Complete questionnaires that will ask about quality of sleep in the ICU and memory, attention and concentration after ICU discharge. These questionnaires will take approximately 20 minutes to complete.
- A family member or a close friend will be asked to complete a questionnaire describing how your memory, attention and concentration were prior to being admitted to the hospital. This will take approximately 10 minutes to complete.

You will be seen in clinic at the University Health Network at 6- and 12-months after your discharge from the ICU. You will be contacted 2-3 weeks before your follow-up appointment to confirm availability. As part of these visits, you will be asked to:

- Provide a 10-20 ml blood sample for biomarkers.
- Wear an actigraph for 10 days, after which time you will return it to the study centre by pre-paid courier.
- Wear stickers on your head to monitor your brain activity for approximately 1 hour.
- Complete questionnaires that will assess your quality of sleep, memory, attention, and concentration, and mood. These will take approximately 10 minutes each to complete.

The entire follow-up appointment should take approximately 2 hours. If preferred, you can have your memory testing done over the phone and the mood questionnaire could be completed at home and mailed. This would decrease your follow-up appointment to less than 90 minutes.

VOLUNTARY PARTICIPATION

The study participant's participation in this study is voluntary. You can choose not to be in the study or you may leave the study at any time without affecting your medical care. Throughout the study, you will be advised of any new information that might affect your decision to remain in the study.

WITHDRAWAL FROM STUDY

If you decide to leave the study, the information that was collected before you leave the study will still be used in order to help answer the research question. No new information will be collected without your permission.

RISKS

This study has risks. Some of these risks we know about. There is also a possibility of risks that we do not know about and have not been seen in study participants to date. Please call the study doctor if you have any side effects even if you do not think it has anything to do with this study. The risks we know of are:

- Blood tests: To reduce and/or minimize any discomfort you may experience, whenever possible, we will take a blood sample while blood is being drawn as part of your standard clinical care. Blood will be taken from either a tube already inserted into your artery or if you do not have this, we will have to take it from a needle inserted into your vein. If the sample is taken using a needle you may experience discomfort or pain, and there may be a small amount of bleeding. You may experience a slight discomfort, bruising, bleeding, swelling or redness at the place of the needle puncture site. There is also a slight chance of infection at the place where the needle punctures your skin.

- The measures of brain activity: During the test to see what happens in the brain, the technician may encourage the patient to do things that stimulate the brain such as deep breathing or flashing lights. As a result, you may feel dizziness or lightheadedness. It is uncommon and will resolve in minutes. Mild irritation can rarely be experienced from the preparation of the skin and cream used to attach the electrodes to the scalp for recordings. This is typically very mild and resolves within hours to days. The glue used to attach electrodes has a bad smell and may cause headaches, irritation of the eyes, rarely a skin reaction. Again, these reactions are usually mild and resolve quickly.

BENEFITS

You may receive no direct benefits from being in this study. However, results from this study may further medical and/or scientific knowledge.

ALTERNATIVES TO BEING IN THE STUDY

If you do not take part in the study, you will be followed up as per clinical care usual schedule.

CONFIDENTIALITY

If you agree to join this study, the study doctor and his/her team will look at your personal health information and collect only the information they need for the study. Personal health information is any information is any information that could identify you and includes your:

- Name,
- Address,
- Date of birth,
- Postal code,
- New or existing medical records that includes types, dates and results of medical tests or procedures.

Only the study team or the people or groups listed below will be allowed to look at your records. Your participation in this study also may be recorded in your medical record at this hospital. This is for clinical safety purposes.

The following people may come to the hospital to look at the study records and at your personal health information to check that the information collected for the study is correct and to make sure the study is following proper laws and guidelines:

- Representatives of the University Health Network (UHN) including the UHN Research Ethics Board

All information obtained during the study will be held in strict confidence. The study participant will be identified with a study number only. No names or identifying information will be used in any publication or presentations. No information identifying you will be transferred outside the investigators in this study or this hospital.

COSTS

You will not have to pay for any of the procedures involved with this study. You will be given 25$ to cover parking for each of the two visits that you make to the hospital for the study.

RIGHTS AS A PARTICIPANT

If you are harmed as a direct result of taking part in this study, all necessary medical treatment will be made available to you at no cost.

By signing this form you do not give up any of your legal rights against the investigators, sponsor or involved institutions for compensation, nor does this form relieve the investigators, sponsor or involved institutions of their legal and professional responsibilities.

CONFLICT OF INTEREST

Researchers have an interest in completing this study. Their interests should not influence your decision to participate in this study.

QUESTIONS ABOUT THE STUDY

If the study participant suffers any side effects or other injuries during the study, or if you have any general questions about the study, please call the doctor in charge of this study, Dr. Elizabeth Wilcox at (416) XXX-XXXX. You may also contact the Medical/Surgical ICU study coordinator at Toronto Western Hospital, Medical/Surgical ICU) at (416) XXX-XXXX or at (416) the Toronto General Hospital at (416) XXX-XXXX, at any time.

If you have any questions about the study participant's rights as a research participant or have concerns about this study, call the Chair of the University Health Network Research Ethics Board (REB) or the Research Ethics office number at (416) 581-XXXX. The REB is a group of people who oversee the ethical conduct of research studies. These people are not part of the study team. Everything that you discuss will be kept confidential.

DOCUMENTATION OF INFORMED CONSENT

Study Title: **COGWELL:** COGnitive Outcomes and WELLness in Survivors of Critical Illness

This study has been explained to me and any questions I had have been answered.
I know that I may leave the study at any time. I agree to take part in this study.

_____	_____	_____
Print Study Participant's Name	Signature	Date

(You will be given a signed copy of this consent form)

My signature means that I have explained the study to the participant named above. I have answered all questions.

_____	_____	_____
Name of participant (print)	Signature	Date

_____	_____	_____
Substitute decision-maker (print)	Signature	Date

_____	_____	_____
Name of Person obtaining consent (print)	Signature	Date

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

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym **(p. 1)**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry **(p. 3 and 14)**
	2b	All items from the World Health Organization Trial Registration Data Set **(N/A)**
Protocol version	3	Date and version identifier **(N/A)**
Funding	4	Sources and types of financial, material, and other support **(p. 15)**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors **(p. 1 and 15)**
	5b	Name and contact information for the trial sponsor **(N/A)**
	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)**
	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) **(p. 13-14)**
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 **(p. 5-7)**
	6b	Explanation for choice of comparators **(N/A)**
Objectives	7	Specific objectives or hypotheses **(p. 8)**

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) **(p. 8)**
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 **(p. 8)**
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) **(p. 19)**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered **(N/A)**
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) **(N/A)**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) **(N/A)**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial **(N/A)**
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended **(p. 9-11)**
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) **(Figure 1)**
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 **(p. 12-13)**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size **(p. 13)**
Methods: Assignment of interventions (for controlled trials)		
Allocation:		

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions **(N/A)**
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned **(N/A)**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions **(N/A)**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how **(N/A)**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial **(N/A)**
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol **(p. 9)**
	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 **(p. 13)**
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 **(p. 13-14)**
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol **(p. 12-13)**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) **(N/A)**
	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	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed **(N/A)**
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial **(N/A)**
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct **(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 **(p. 14)**
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) **(p. 9)**
	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 **(p. 14)**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site **(p. 15)**
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators **(p. 14)**
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation **(N/A)**

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions **(p. 14)**
	31b	Authorship eligibility guidelines and any intended use of professional writers **(N/A)**
	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 **(Appendix)**
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable **(N/A)**

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

BMJ Open

A study protocol for an observational cohort investigating COGnitive outcomes and WELLness in survivors of critical illness: the COGWELL study

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A study protocol for an observational cohort investigating COGnitive outcomes and WELLness in survivors of critical illness: the COGWELL study

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ABSTRACT

Introduction: Up to 9 out of 10 ICU survivors will suffer some degree of cognitive impairment at hospital discharge and approximately half will have decrements that persist for years. While the mechanisms for this newly acquired brain injury are poorly understood. The purpose of this study is to describe the prevalence of sleep abnormalities and their association with cognitive impairment, examine a well-known genetic risk factor for dementia (APOE ε4) that may allow for genetic risk stratification of ICU survivors at greatest risk of cognitive impairment, and determine if EEG is an independent predictor of long-term cognitive impairment, and possibly a candidate intermediate end point for future clinical trials.

Methods and Analysis: This is a multisite, prospective, observational cohort study. The setting for this trial will be medical and surgical intensive care units of five large tertiary care referral centres. The participants will be adult patients admitted to a study ICU and invasively ventilated for ≥3 days who survive to hospital discharge. Participants will undergo follow-up within 7 days of ICU discharge, 6-months, and 1-year. At each time point patients will have an EEG, blood work (biomarkers; gene studies), sleep study (actigraphy), complete a number of questionnaires, as well as undergo neuropsychological testing. The primary outcome of this study will be long-term cognitive function at 12-months follow-up as measured by the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and Trails Making Test B.

Ethics and Dissemination: The study has received the following approvals: University Health Network Research Ethics Committee (13-6425-BE), Sunnybrook Health Centre Research Ethics Committee (365-2013), Mount Sinai Research Ethics Committee (14-0194-E), and St. Michael's Hospital Research Ethics Committee (14-295). Results will be made available to critical care survivors, their caregivers, the funders, the critical care societies, and other researchers. This study is registered with ClinicalTrials.gov (NCT02086877).

STRENGTHS AND WEAKNESSES

- COGWELL will provide the first multisite, comprehensive study to investigate sleep and circadian function, rhythmic cortical electrophysiological activity measured by quantitative EEG, and long-term cognitive impairment in survivors of critical illness.
- Our longitudinal study design will allow us to look at changes over time in the same patient, defining the temporal sequence of changes, and providing stronger evidence for causality.

- Based on strong scientific reasoning from other patient populations, if true our genomic association theory would provide a way of identifying susceptible individuals who may benefit most from intervention strategies.
- The primary limitation of this study is loss to follow-up and missing data points that would challenge the internal validity of reported results from COGWELL.

BACKGROUND

Context

Cognitive outcomes have been evaluated in various ICU patient populations; mixed critically ill patients who required prolonged mechanical ventilation[1, 2], survivors of sepsis and septic shock[3, 4] and medical patients who underwent elective surgery[5]. Impaired cognition was seen in several domains at varying time periods. Cognitive impairment was seen in 39-91% of patients at hospital discharge, 13-79% at 3 to 6 months follow-up and 20-71% at 1 year[6]. Little is known regarding the interactions between identifiable risk factors (host factors and acute events in the ICU and after ICU discharge), and cognitive function after critical illness. Moreover, there are few objective tools with which to risk stratify patients with regard to persistent cognitive dysfunction. Identifying objective risk factors and risk markers are first steps towards developing and effectively targeting interventions to prevent post-ICU cognitive impairment.

Current Knowledge

Sleep disorders

There is considerable evidence linking sleep disordered breathing and poor sleep quality with cognitive impairment in a variety of patient populations[7-11]. Cognitive domains particularly associated with sleep disruption include working memory, semantic memory, processing speed, and visuospatial abilities[8]. Experimental studies support a number of potential neurobiological mechanisms including accumulation of beta amyloid pathology[12, 13], abnormalities of tau[7], synaptic abnormalities[14], changes in hippocampal long term potentiation[15], impaired hippocampal neurogenesis[16, 17], and gene expression changes[18]. The appeal of sleep and circadian dysfunction as potential mechanisms mediating post-ICU cognitive impairment is that effective interventions exist to improve sleep and circadian function.

Few studies have rigorously evaluated the prevalence of sleep disruption after critical illness, and its potential role in potentiating cognitive impairment. A prospective multicenter cohort study (n=1625), reported no change in self-reported sleep quality in the year following critical illness using a non-validated single instrument assessment[19]. However, subjective reports of sleep quality can be confounded by poor recall and misperception. A second small case series reported sleep disruption and poor sleep efficiency as measured by polysomnography in five out of seven survivors of ARDS each of whom reported sleep difficulties 6 months after hospital discharge[20]. Neither study reported cognitive outcomes. A study demonstrating the prevalence of sleep abnormalities after critical illness

and their longitudinal association with cognitive impairment would yield potential targets for therapy and novel endpoints for ICU based studies.

Proteomics and Genomics

The Apolipoprotein E (*APOE*) ε4 allele is a well-established and common genetic risk factor for Alzheimer disease[21-23], and is also a risk factor for cognitive impairment in a number of medical conditions including sleep apnea[11, 24, 25] and following repeated head trauma[26]. Recently, in a longitudinal cohort of 737 community dwelling older adults without dementia, the *APOE* ε4 allele was shown to accentuate the impact of sleep fragmentation on the risk of incident Alzheimer's disease in older persons, an effect that was mediated by the accumulation of tau pathology[7, 27]. In individuals with high sleep fragmentation, the presence of at least one *APOE* ε4 allele (*APOE* ε4 +/- or +/+) was associated with a three times faster rate of cognitive decline as compared to individuals not carrying an APOE ε4 allele (*APOE* ε4 -/-)[7].

Although there are no large studies of genetic susceptibility to cognitive impairment following critical illness, data suggest the APOE ε4 allele can have dramatic effects on the acute cognitive status of critically ill patients. In one study, the APOE ε4 allele was associated with a seven-fold increase in the odds of a long duration of delirium (OR 7.3; 95% CI, 1.8 – 30)[28]. The presence of APOE ε4 was found to have a stronger association with duration of delirium than age, severity of illness score (APACHE II), sepsis or benzodiazepine use[28]. Although the duration of delirium is associated with worse cognitive performance after the ICU, the specific role of the APOE ε4 genotype in this association is unknown. Recent work in non-critically ill elderly patients found that administration of benzodiazepines in healthy elderly subjects (n=42) with the APOE ε4 allele was associated with more pronounced cognitive impairment and slower to recover cognitive functioning[29, 30]. This association was found to be independent of deranged pharmacokinetics. Thus, the possibility arises that APOE ε4 may herald a more pronounced vulnerability to a number of brain insults, including drug-related brain toxicity.

This study may identify *APOE* genotype as a biological marker of susceptibility to cognitive impairment and the disruptive effects on sleep following ICU discharge. If this is true, then *APOE* ε4 positive individuals may represent a subpopulation of critical illness survivors who may benefit form particularly close cognitive monitoring and early intervention to improve sleep and circadian function.

Neurophysiology

Studies have so far been unable to identify patients at higher risk of long-term cognitive impairment using screening tools at hospital discharge. For example, in a study by Woon and colleagues, neither the Folstein Mini Mental Status Examination (MMSE) or MiniCog performance at hospital discharge predicted cognitive impairment at 6-month follow-up[31]. Performance on more sensitive tests of cognitive impairment may have predictive value, but these have not been evaluated. This lack of predictive ability restricts the capacity of clinicians and researchers to adequately risk stratify patients with regard to the likelihood of cognitive impairment.

One candidate predictor for cognitive impairment is quantitative electroencephalography (EEG). Serial quantitative EEG has been used to diagnose delirium in older patients (n=25) with and without underlying dementia on an inpatient geriatric psychiatry service[32]. Not only did quantitative EEG (amount of slow wave activity in theta and delta frequencies) prove sensitive, as compared to the clinical exam, for the diagnosis of delirium across a range of underlying etiologies (medication intoxication, hypoxia, and electrolyte disturbances, etc.), it also measured severity of delirium. In the ICU, quantitative EEG has also been found to be a sensitive predictor of mortality in patients with severe sepsis, with well-defined categories (numerical and qualitative variables: no encephalopathic changes, mild encephalopathy and severe encephalopathy) of progressively slower EEG waveforms associated with an increased risk of death, with the highest risk associated with burst suppression[33, 34]. Similar findings were found in a prospective observational study in medical ICU patients, where burst suppression was found to be an independent predictor of death at 6 months[35]. Finally, a recent case series of sepsis survivors showed EEG to be a possible candidate predictor of cognitive impairment. Deficits in verbal learning and memory were associated with low-frequency activity on routine EEG at 6 to 24 months following hospital discharge (indicative of nonspecific brain dysfunction)[4]. This study is supportive of our study hypothesis but is insufficient to answer the question of whether EEG could be used as a predictive tool in studying cognitive function after critical illness as it was limited by small sample size (n=25) and inadequate control of time, as follow-up was not standardized (single data collection point per patient; range of 6-24 months)[4].

Although it is likely an imperfect tool, EEG may be able to provide prognostic information. If quantitative EEG is linked with long-term cognitive outcomes, it may serve as a good intermediate

endpoint in therapeutic trials assessing interventions to decrease the risk of post-ICU cognitive impairment.

Study Aims

Research hypothesis and aims

We hypothesize that critical illness will be associated with decrements in sleep and circadian function, quantifiable by actigraphy, that are in turn associated with worse cognitive performance in ICU survivors at 6 and 12 months after hospital discharge. Second, APOE genotype will be a risk factor for cognitive impairment following a number of brain insults (e.g. intermittent hypoxia, sleep disruption) and may modify the effect of sleep fragmentation on cognition in ICU survivors. APOE genotype may help predict the trajectory of recovery from critical illness, specifically with respect to cognitive impairment. Finally, we hypothesize that survivors of critical illness with cognitive dysfunction will have a greater proportion of low frequency vs. high frequency cortical electrophysiological activity compared to survivors without cognitive dysfunction. EEG will be a predictor of long-term cognitive impairment and therefore could serve as a surrogate endpoint for clinical trials.

To test our first hypothesis, we will determine the impact of sleep and circadian disruption on long-term cognitive impairment in survivors of critical illness. Further, we will determine the relationship between the APOE genotype, sleep disruption and cognitive impairment in a cohort of survivors of critical illness. This is an exploratory aim to examine for direct associations between *APOE* genotype and cognitive function, as well as for gene and environment interaction (e.g. *APOE* and sleep fragmentation interaction) effects on cognitive function. Lastly, we will determine the relationship between rhythmic cortical electrophysiological activity, measured by serial quantitative EEG, and long-term cognitive outcomes in a cohort of patients who have survived critical illness and are clinically stable prior to hospital discharge.

METHODS AND ANALYSIS

Study protocol

This is a multisite, prospective, observational cohort study involving five teaching hospitals (Toronto Western Hospital, Toronto General Hospital, St. Michael's Hospital, Mount Sinai Hospital, and Sunnybrook Health Sciences Centre) at the University of Toronto. Study patients will enter the cohort after they have been mechanically ventilated for at least 3 days, after they meet inclusion/exclusion

criteria (see Table 1), and they have survived to ICU discharge. Trained research personnel will obtain informed consent from the patient or their next of kin (See Supplementary file). Patients will leave the cohort one year after discharge from ICU or at the time of death.

At the time of enrollment, we will record the following data: baseline demographic, admission diagnosis and dates, severity of illness (APACHEII); burden of comorbid illness using Charlson[36] and Elixhauser[37] comorbidities scores; pre-existing cognitive impairment by Informant Questionnaire on Cognitive Decline in the Elderly Short Form (IQCODE-SF); intensive care unit (ICU) and hospital length of stay (LOS).

Study personnel blinded to study hypothesis will prospectively collect data on important confounders such as hemodynamic and ventilator parameters, glycemic control and the presence or absence of delirium on a daily basis. At the time of study enrollment, information collected on each patient will include the following: APACHE II disease category, patient demographics, dates of hospital and ICU admission, initial date of mechanical ventilation, admission diagnosis, history of comorbid disease(s) present at the time of ICU admission captured by the Charlson and Elixhauser Comorbidity Scales and preexisting dementia by the IQCODE-SF. During the course of each patient's stay in the ICU data will be collected on: acute lung injury score (LIS), Sequential Organ Failure Assessment Score (SOFA), and APACHE II score; mean partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2), central venous pressure, mean arterial pressure and blood glucose, daily mean Riker's sedation agitation score, Confusion Assessment Method in the ICU (CAM-ICU) status and average daily doses of the following medications: benzodiazepines, propofol, narcotics, and dexmedetomidine. All patients will undergo standardized follow-up prior to hospital discharge, and at 6- and 12-months. Outcome variables will be collected at each time point (See Figure 1). A trained assessor blinded to our study hypothesis will perform all cognitive assessments. Study participants will be identified with a study number only. No identifying information will be transferred outside of the participating hospital site.

Measurement of Exposures and Confounders

Actigraphy:

Actigraphy is the continuous measurement of an individual's movement using a wristwatch-like device (Actiwatch Spectrum, Phillips Respironics, Bend, OR) and is an objective method of quantifying sleep and circadian rhythms. It has been validated against polysomnography for the measurement of total

sleep time and sleep fragmentation[7, 38] and validated against biochemical markers for the assessment of circadian rhythmicity[39]. All patients will have an actigraph placed on their nondominant wrist days within 1 week of ICU discharge. Recordings will continue while on the inpatient ward; however, the number of days of actigraphic data recorded in hospital is likely to vary depending on severity of illness and trajectory of recovery. If patients are discharged home or to a rehabilitation facility prior to attaining 10 days of actigraphic data, the patient will be asked to continue the recording and return the actigraph to the study centre by pre-paid courier. Patients will return to follow-up clinic at 6- and 12-months where actigraphs will be worn again for 10 days as an outpatient.

All actigraph data will be analyzed using MATLAB (Mathworks, Natick, MA). Markers of sleep and circadian function will include: (1) circadian timing (average time of the activity acrophase [midpoint of 8 consecutive hours] of each 24 hours of greatest activity), (2) sleep duration (determined by the Cole-Kripke algorithm), (3) sleep fragmentation (quantified by K_{RA})[7, 8, 40], and (4) regularity of circadian rhythmicity (determined using the chi-square periodogram)[41].

Richards-Campbell Sleep Questionnaire (RCSQ):

This is a five-item, visual analogue scale designed to assess the perception of sleep in critically ill patients[42]. The scale evaluates perceptions of depth of sleep, sleep onset latency, number of awakenings, time spent awake, and overall sleep quality. Patients will complete the questionnaire as they reflect on their last night's stay in the ICU prior to ward discharge.

Pittsburgh Sleep Quality Index:

The Pittsburgh Sleep Quality Index (PSQI) is a self-rated questionnaire, assessing sleep quality over a 1-month time interval. Nineteen individual items generate seven "component" scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The sum of scores for these seven components yields one global score; a global PSQI score greater than 5 yielded a diagnostic sensitivity of 89.6% and specificity of 86.5% in distinguishing good and poor sleep quality[43]. Patients will complete the questionnaire first, while in hospital, to identify any pre-existing sleep disorders (reporting on their sleep the month prior to hospitalization) and then again at 6- and 12-months, reporting perceived reasons for impaired sleep, if any, the month prior to each follow-up appointment.

Genomics [APOE]:

The APOE coding single-nucleotide polymorphism (SNP) sites rs7412 and rs429358 will be determined using the Invitrogen Snapshot assay at The Centre for Applied Genomics at The Hospital for Sick Children Hospital (Toronto, ON; www.tcag.ca). Blood samples (5-10 ml) will be drawn prior to discharge in a lavender top ethylenediaminetetraacetic acid tube. Blood will be stored at -20°C prior to being shipped for testing at The Hospital for Sick Children Hospital.

EEG:

Within 7 days after ICU discharge, approximately 30 minutes of EEG activity will be digitally acquired (XLTEK, Oakville, ON) with electrodes placed according to the international 10–20 system with additional surface sphenoidal electrodes. In outpatient follow-up, at 6- and 12-months, 30 minutes of EEG activity will be recorded. Data sampling will occur at a rate of 256 Hz. Power spectra will be calculated for consecutive 4-s windows for each electrode contact, and absolute spectral band power for conventional EEG frequency bands (δ: 0.5–4 Hz; θ: 4–8 Hz; α: 8–13 Hz; β: 13–20 Hz; γ: 20–40 Hz) will be averaged across different windows. Given that global changes are expected, the band power values will be averaged over all electrode contacts. Similar measures have been previously used to characterize Alzheimer's disease and depression and, in the former, were correlated with clinical measures of severity of dementia[44-46].

Beck's Depression Inventory (BDI-II):

This instrument screens for depression using criteria consistent with the Diagnostic and Statistical Manual of Mental Disorders- Fourth Edition. Higher scores (range, 0-63) indicate more depressive symptoms. Based on testing in psychiatric outpatients, depression symptom severity is classified as minimal (score, 0-13), mild (score, 14-19), moderate (score, 20-28), and severe (score, 29-63)[47]. The BDI-II will be performed after each neuropsychological assessment as depression could confound our primary outcome, cognition. Recently, the BRAIN-ICU study, a prospective cohort of mixed medical, surgical and cardiac patients, reported that regardless of age, executive dysfunction was independently associated with subsequent worse severity of depressive symptoms and worse mental health related quality of life[48].

The Informant Questionnaire on Cognitive Decline in the Elderly Short Form (IQCODE-SF):

The IQCODE-SF is a brief questionnaire that uses information provided by an informant (typically a close relative) to assess a person's change in cognitive functioning over the preceding ten years. The questionnaire is often used as a screening test to detect dementia. The standard method used to

generate the test score is to take the average rating across 16 situations. A person who has no cognitive decline will have an average score of 3, while scores of greater than 3 indicate that some decline has occurred[49].

Measurement of Outcomes: Long-Term Cognitive Morbidity

Repeatable Battery for the Assessment of Neuropsychological Status (RBANS):

The RBANS is a comprehensive and validated neuropsychometric battery for the evaluation of global cognition, including individual domains of immediate and delayed memory, attention, visuospatial construction, and language[50]. The population age-adjusted mean (± SD) for the RBANS global cognition score and for the individual domains is 100 ± 15 (on a scale ranging from 40 to 160, with lower scores indicating worse performance). The RBANS has been validated in diverse patient populations including those with mild cognitive impairment, moderate to severe traumatic brain injuries, vascular dementias, and Alzheimer's Disease[51-54].

Trailing Making Tests A and B:

Executive function (specifically, cognitive flexibility) will be tested using the Trail Making tests A and B; age-, sex-, and education-adjusted mean T score is 50 (range 0 to 100), with lower score indicating poor performance[55].

Telephone Interview for Cognitive Status (TICS):

The TICS instrument will be used as a secondary means to assess cognitive outcome prior to hospital discharge, as well as at 6- and 12-month follow-up. It is made of 11 test items: 10 word immediate and delayed recall tests of memory, a serial 7s subtraction test of working memory, counting backwards to assess attention and processing speed, an object naming test to assess language, and recall of the date and US president [or Canadian prime minister] to assess orientation[56]. Composite scores using all the items create a measure of cognitive functioning, which can range from 0 to 35. It takes approximately 10 minutes to administer and score. T-scores are based on normative data from 6,726 persons[56]. In an effort to minimize loss to follow-up when in depth neuropsychological testing can't be performed due to patient time pressures we will administer this less burdensome instrument. The TICS tool has been extensively validated; it was the cognitive assessment tool used in the Health and Retirement Study [HRS] to make national estimates of dementia and cognitive impairment without dementia [CIND] in the US [n=30,000][57]. Its performance was determined against a detailed neuropsychological and clinical assessment in a

smaller subsample. The overall levels of dementia and of CIND estimated using TICS was similar to those directly estimated from the neuropsychological study. The TICS was found however to be less sensitive at discriminating between normal cognitive function and mild cognitive impairment[58].

Statistical Analysis Plan

Assessing the epidemiology of long-term cognitive impairment will focus on prevalence, severity and natural history. Prevalence will be determined based on binary assessment of patient having or not having clinically significant cognitive impairment, defined as test scores 1 standard deviations (SD) below the population mean on the RBANS global cognition score. We will screen the covariates using the univariate association between the outcome and level of education, RCSQ and PSQI scores, BDI-II, hospital LOS, and days of mechanical ventilation and selecting those with $p<0.2$. Logistic regression analysis models will be used to determine the association between sleep fragmentation and cognitive impairment at 1-year while adjusting for the variables selected. We will enter into the model only those covariates that are not multicollinear based on the variance inflation factor criterion. Given that we predict we will have approximately 30 events at the 1-year follow-up, this will give us at least 5 events per variable[59].

Generalized estimating equations (GEE) models, to take into account the correlation between the 3 measurements per subject, will be used to determine the association of EEG and the effect of time on cognitive impairment. We will test the association between APOE ε4(+/- or +/+) versus APOE ε4(-/-) and cognitive impairment using χ^2 test. The degree of association between APOE and sleep efficiency will be determined using Spearman's correlation; this information will be used to inform future trials.

We calculated our sample size based on logistic regression analysis with outcome cognitive impairment at 12 months. We used a proportion of 30% cognitive impairment at 1-year in this patient population. We do not know a priori the association between our sleep efficiency variable and the other covariates so we will use a range of R-squared (R-squared obtained by regressing the sleep efficiency variable on the other covariates) from low to moderate (0.1 to 0.5). With a sample size of approximately 110, we have 80% power with α=0.05 for R-squared=0.5 to detect an absolute increase in percentage of cognitive impairment of 20% (from 30% to 50%) for a decrease in sleep efficiency value with one standard deviation from the mean or an increase of 15% (from 30 to 45%)

for a R-squared=0.2. With 110 patients, approximately 20% in the APOE ε4(+/- or +/+) group, a χ^2 test at α=0.05 will be able to detect a 37.5% difference (25% in the APOE ε4[-/-] group and 62.5% in the APOE ε4[+/- or +/+] group) in the cognitive impairment group with about 92% power or about 80% power to detect a difference of 31% (25% in the APOE ε4[-/-] group versus 56% in the APOE ε4[+/- or +/+] group).

A total of approximately 150 patients will be consented to participate. This estimate is based on a calculated 1-year mortality rate of 15% in patients discharged from critical care units and a conservative loss to follow-up rate of 15%.

Methodological Issues

Our longitudinal study design, in which parallel covariates are reliably and repeatedly measured over time, will allow us to look at changes over time in the same patient, defining the temporal sequence of changes, and providing stronger evidence for causality than could be obtained from a cross-sectional design. Although our genomic association theory is an exploratory aim, it is based on strong scientific reasoning from other patient populations and if our hypothesis is true, would provide an easy way of identifying susceptible individuals who may benefit the most from interventions to decrease the risk of cognitive impairment.

The primary limitation of this study is loss to follow-up and missing data points that would challenge the internal validity of reported results from COGWELL. However, our research team has extensive experience in achieving high follow-up rates in similar studies of cognitive function and long-term follow-up of critically ill patients[60-64]. Efforts to minimize loss to follow-up will include respecting the time commitment of patients, formal tracking procedures of patients enrolled including acquiring of multiple contacts for arranging follow-up, strong interpersonal skills of study personnel, and flexible hours for testing[65].

Data Management and Oversight

Site investigators will take responsibility for the conduct of COGWELL. Site investigators will supervise the day-to-day operation of the project, and are responsible for ensuring that International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines are followed.

Members of the COGWELL research team from the University Health Network will monitor the data. Members will review the first three completed charts from each site as well as a random sample of 10% of completed data thereafter. Monitoring will ensure protocol compliance, proper study management, and timely completion of study procedures.

Data Sharing

The final trial dataset will be available to study investigators, Steering Committee members and the Research Ethic Boards at all participating sites.

ETHICS AND DISSEMINATION

The study has received the following approvals: University Health Network Research Ethics Committee (13-6425-BE), Sunnybrook Health Centre Research Ethics Committee (365-2013), Mount Sinai Research Ethics Committee (14-0194-E), and St. Michael's Hospital Research Ethics Committee (14-295). Using traditional and innovative methods, the results will be made available to critical care survivors, their caregivers, the funders, the critical care societies, and other researchers.

Protocol and Registration

This study is registered with ClinicalTrials.gov (NCT02086877).

Patient Anonymity

A unique study number will identify study participants. Identity of the study participant will be recorded and secured in a locked office with access limited to study personnel. The study data will be anonymized at the time of collection. The data collection form will be destroyed at the end of the study once the data has been published. The principal investigator will destroy the study enrollment log once all results have been verified and published (a minimum of 5 years).

Data storage and security

Data will be stored on institutional network drives with firewalls and security measures in place. Hard copy records will be stored in a locked cabinet in a secure location. Access to records and data will be limited to study personnel. Study data will be de-identified and a master linking log with identifiers will be kept and stored separately from the data.

Contributions

The study concept and design was conceived by MEW, ASL, MPM, RAW, SEB and GDR. KDW, MST, JOF and MEW will conduct screening and data collection. Analysis will be performed by RLP. MEW prepared the first draft of the manuscript. All authors provided edits and critiqued the manuscript for intellectual content.

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Competing Interests
None declared.

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Table 1. Inclusion and Exclusion Criteria

Inclusion criteria	• ≥16 years of age • Admission to study ICU for invasive mechanical ventilation [≥ 3 days]
Exclusion criteria	• Advanced cognitive impairment or unable to follow simple commands before their acute illness [e.g. end-stage Alzheimer's disease] • Primary neurological injury [e.g. anoxic injury, stroke or traumatic brain injury] • Anticipated death within 3 months of discharge [e.g. palliative] • Uncontrolled psychiatric illness at hospital admission • Not fluent in English • Unlikely to adhere with follow-up [e.g. no fixed address] • Residence greater than 300 kms from referral centre

Figure 1. Flow diagram of the Cognitive Outcome and Wellness in survivors of critical illness (COGWELL) study.

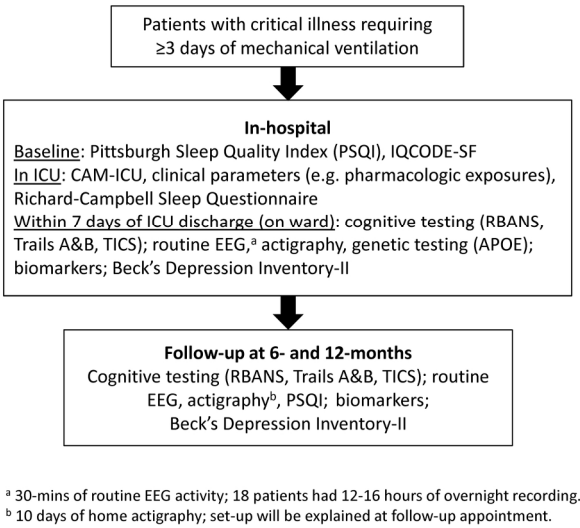

Figure 1. Flow diagram of the Cognitive Outcome and Wellness in survivors of critical illness (COGWELL) study.

190x142mm (300 x 300 DPI)

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CONSENT TO PARTICIPATE IN A RESEARCH STUDY

STUDY TITLE: **COGWELL:** COGnitive outcomes and WELLness in survivors of critical illness

PRINCIPAL INVESTIGATOR (Study Doctor): **Dr. M. Elizabeth Wilcox**
Toronto Western Hospital
Telephone: 416-603-5800 ext. XXXX

24-HOUR PHONE NUMBER: **Toronto Western Hospital ICU**
Telephone: 416-603-XXXX
(Ask for the attending physician on call)

This consent is directed to the patient, but, in the event that the patient is unable to give consent on his/her behalf, a next-of-kin or legal representative may provide consent on the patient's behalf.

INTRODUCTION

You are being asked to take part in a research study. Please read this explanation about the study and its risks and benefits before you decide if you would like to take part. You should take as much time as you need to make your decision. You should ask the study doctor or study staff to explain anything that you do not understand and make sure that all of your questions have been answered before signing this consent form. Before you make your decision, feel free to talk about this study with anyone you wish including your friends, family, and family doctor. Participation in this study is voluntary. Regardless of your decision, you will continue to receive the best care possible at the University Health Network.

BACKGROUND/PURPOSE

You are being asked to take part in this study because you have an acute illness that required mechanical ventilation in the intensive care unit (ICU). There is currently little information available on the long-term outcomes after ICU. Up to 9 out of 10 patients may experience problems with their memory and attention, and in approximately half of patients these problems can last for years. Two important questions are 1) whether or not we can predict which patients will have memory or attention problem years later and 2) are there things that can be done to minimize the effect of critical illness on memory and attention?

STUDY DESIGN

The purpose of this study is to learn what the one-year memory, attention and concentration, and day-to-day function (ability to balance check book, make a shopping list, etc.) is in patients who have been on a mechanical ventilator for at least 3 days. We also want to see how sleep quality and different blood changes may affect one-year performance on these tests. Lastly, this study wants to see if a routine test to measure brain activity can predict who will have memory, attention and concentration, and day-to-day function at one-year follow-up.

While in the ICU, you have received standard care as required by your diagnosis and clinical symptoms. Taking part in the study does not involve changes in the care that you will be receiving while at the University Health Network. If you choose to take part, a set of tests will be done in addition to those routinely done during your hospital stay.

The Apolipoprotein E (APOE) blood test is a test for genetic risk factors for Alzheimer's disease. The sample will be taken to check for the relationship between APOE and sleep disruption and memory, attention, and concentration in survivors of critical illness. This sample will be collected while you are still in hospital and sent to the Hospital for Sick Children, Toronto, ON for analysis. Another blood sample will be tested to see how the activity of the immune system changes over time after critical illness. This sample will be stored at the University Health Network and then tested at the University of Toronto. The results of these tests will not be available to study participants. The blood samples will be destroyed after the testing is done.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 150 patients will be taking part in this study. Of those 150 patients, around 100 will be at the University Health Network.

PROCEDURES

Study visits:

Within the first week after discharge from the ICU, if you are able, you will be asked to:

- Provide a 10-20 ml blood sample for two blood tests: the APOE and biomarkers.
- Wear a wristwatch-like device (actigraph) for 10-days to measure continuously your movement to assess amount and quality of your sleep.
- Stickers will be put on your head to monitor your brain activity during the day or early evening (approximately 1 hour).
- Complete questionnaires that will ask about quality of sleep in the ICU and memory, attention and concentration after ICU discharge. These questionnaires will take approximately 20 minutes to complete.
- A family member or a close friend will be asked to complete a questionnaire describing how your memory, attention and concentration were prior to being admitted to the hospital. This will take approximately 10 minutes to complete.

You will be seen in clinic at the University Health Network at 6- and 12-months after your discharge from the ICU. You will be contacted 2-3 weeks before your follow-up appointment to confirm availability. As part of these visits, you will be asked to:

- Provide a 10-20 ml blood sample for biomarkers.
- Wear an actigraph for 10 days, after which time you will return it to the study centre by pre-paid courier.
- Wear stickers on your head to monitor your brain activity for approximately 1 hour.
- Complete questionnaires that will assess your quality of sleep, memory, attention, and concentration, and mood. These will take approximately 10 minutes each to complete.

The entire follow-up appointment should take approximately 2 hours. If preferred, you can have your memory testing done over the phone and the mood questionnaire could be completed at home and mailed. This would decrease your follow-up appointment to less than 90 minutes.

VOLUNTARY PARTICIPATION

The study participant's participation in this study is voluntary. You can choose not to be in the study or you may leave the study at any time without affecting your medical care. Throughout the study, you will be advised of any new information that might affect your decision to remain in the study.

WITHDRAWAL FROM STUDY

If you decide to leave the study, the information that was collected before you leave the study will still be used in order to help answer the research question. No new information will be collected without your permission.

RISKS

This study has risks. Some of these risks we know about. There is also a possibility of risks that we do not know about and have not been seen in study participants to date. Please call the study doctor if you have any side effects even if you do not think it has anything to do with this study. The risks we know of are:

- Blood tests: To reduce and/or minimize any discomfort you may experience, whenever possible, we will take a blood sample while blood is being drawn as part of your standard clinical care. Blood will be taken from either a tube already inserted into your artery or if you do not have this, we will have to take it from a needle inserted into your vein. If the sample is taken using a needle you may experience discomfort or pain, and there may be a small amount of bleeding. You may experience a slight discomfort, bruising, bleeding, swelling or redness at the place of the needle puncture site. There is also a slight chance of infection at the place where the needle punctures your skin.

- The measures of brain activity: During the test to see what happens in the brain, the technician may encourage the patient to do things that stimulate the brain such as deep breathing or flashing lights. As a result, you may feel dizziness or lightheadedness. It is uncommon and will resolve in minutes. Mild irritation can rarely be experienced from the preparation of the skin and cream used to attach the electrodes to the scalp for recordings. This is typically very mild and resolves within hours to days. The glue used to attach electrodes has a bad smell and may cause headaches, irritation of the eyes, rarely a skin reaction. Again, these reactions are usually mild and resolve quickly.

BENEFITS

You may receive no direct benefits from being in this study. However, results from this study may further medical and/or scientific knowledge.

ALTERNATIVES TO BEING IN THE STUDY

If you do not take part in the study, you will be followed up as per clinical care usual schedule.

CONFIDENTIALITY

If you agree to join this study, the study doctor and his/her team will look at your personal health information and collect only the information they need for the study. Personal health information is any information is any information that could identify you and includes your:

- Name,
- Address,
- Date of birth,
- Postal code,
- New or existing medical records that includes types, dates and results of medical tests or procedures.

Only the study team or the people or groups listed below will be allowed to look at your records. Your participation in this study also may be recorded in your medical record at this hospital. This is for clinical safety purposes.

The following people may come to the hospital to look at the study records and at your personal health information to check that the information collected for the study is correct and to make sure the study is following proper laws and guidelines:

- Representatives of the University Health Network (UHN) including the UHN Research Ethics Board

All information obtained during the study will be held in strict confidence. The study participant will be identified with a study number only. No names or identifying information will be used in any publication or presentations. No information identifying you will be transferred outside the investigators in this study or this hospital.

COSTS

You will not have to pay for any of the procedures involved with this study. You will be given 25$ to cover parking for each of the two visits that you make to the hospital for the study.

RIGHTS AS A PARTICIPANT

If you are harmed as a direct result of taking part in this study, all necessary medical treatment will be made available to you at no cost.

By signing this form you do not give up any of your legal rights against the investigators, sponsor or involved institutions for compensation, nor does this form relieve the investigators, sponsor or involved institutions of their legal and professional responsibilities.

CONFLICT OF INTEREST

Researchers have an interest in completing this study. Their interests should not influence your decision to participate in this study.

QUESTIONS ABOUT THE STUDY

If the study participant suffers any side effects or other injuries during the study, or if you have any general questions about the study, please call the doctor in charge of this study, Dr. Elizabeth Wilcox at (416) XXX-XXXX. You may also contact the Medical/Surgical ICU study coordinator at Toronto Western Hospital, Medical/Surgical ICU) at (416) XXX-XXXX or at (416) the Toronto General Hospital at (416) XXX-XXXX, at any time.

If you have any questions about the study participant's rights as a research participant or have concerns about this study, call the Chair of the University Health Network Research Ethics Board (REB) or the Research Ethics office number at (416) 581-XXXX. The REB is a group of people who oversee the ethical conduct of research studies. These people are not part of the study team. Everything that you discuss will be kept confidential.

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DOCUMENTATION OF INFORMED CONSENT

Study Title: **COGWELL:** COGnitive Outcomes and WELLness in Survivors of Critical Illness

This study has been explained to me and any questions I had have been answered.
I know that I may leave the study at any time. I agree to take part in this study.

_____	_____	_____
Print Study Participant's Name	Signature	Date

(You will be given a signed copy of this consent form)

My signature means that I have explained the study to the participant named above. I have answered all questions.

_____	_____	_____
Name of participant (print)	Signature	Date

_____	_____	_____
Substitute decision-maker (print)	Signature	Date

_____	_____	_____
Name of Person obtaining consent (print)	Signature	Date

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

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym **(p. 1)**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry **(p. 3 and 14)**
	2b	All items from the World Health Organization Trial Registration Data Set **(N/A)**
Protocol version	3	Date and version identifier **(N/A)**
Funding	4	Sources and types of financial, material, and other support **(p. 15)**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors **(p. 1 and 15)**
	5b	Name and contact information for the trial sponsor **(N/A)**
	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)**
	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) **(p. 13-14)**
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 **(p. 5-7)**
	6b	Explanation for choice of comparators **(N/A)**
Objectives	7	Specific objectives or hypotheses **(p. 8)**

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) **(p. 8)**
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 **(p. 8)**
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) **(p. 19)**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered **(N/A)**
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) **(N/A)**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) **(N/A)**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial **(N/A)**
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended **(p. 9-11)**
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) **(Figure 1)**
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 **(p. 12-13)**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size **(p. 13)**
Methods: Assignment of interventions (for controlled trials)		
Allocation:		

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions **(N/A)**
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned **(N/A)**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions **(N/A)**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how **(N/A)**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial **(N/A)**
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol **(p. 9)**
	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 **(p. 13)**
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 **(p. 13-14)**
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol **(p. 12-13)**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) **(N/A)**
	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	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed **(N/A)**
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial **(N/A)**
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct **(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 **(p. 14)**
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) **(p. 9)**
	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 **(p. 14)**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site **(p. 15)**
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators **(p. 14)**
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation **(N/A)**

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions **(p. 14)**
	31b	Authorship eligibility guidelines and any intended use of professional writers **(N/A)**
	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 **(Appendix)**
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable **(N/A)**

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