BMJ Open

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

M Elizabeth Wilcox,[1] Andrew S Lim,[2] Mary P McAndrews,[3] Richard A Wennberg,[4] Ruxandra L Pinto,[5] Sandra E Black,[2] Karolina D Walczak,[1] Jan O Friedrich,[6] Michael S Taglione,[1] Gordon D Rubenfeld[5]

CrossMark

For numbered affiliations see end of article.

Correspondence to
Dr M Elizabeth Wilcox; elizabeth.wilcox@utoronto.ca

ABSTRACT

Introduction Up to 9 out of 10 intensive care unit (ICU) survivors will suffer some degree of cognitive impairment at hospital discharge and approximately half will have decrements that persist for years. 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 (Apolipoprotein E ε4) that may allow for genetic risk stratification of ICU survivors at greatest risk of cognitive impairment and determine if electroencephalography (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 ICUs of five large tertiary care referral centres. The participants will be adult patients admitted to a study ICU and invasively ventilated for ≥3 days. 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 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.

Trial registration number NCT02086877; Pre-results.

BACKGROUND
Context
Cognitive outcomes have been evaluated in various intensive care unit (ICU) patient populations: mixture of patients who are

Strengths and weaknesses of this study

► COGWELL will provide the first multisite, comprehensive study to investigate sleep and circadian function, rhythmic cortical electrophysiological activity measured by quantitative electroencephalography 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.

critically ill and 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 3–6 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 multicentre 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 Acute Respiratory Distress Syndrome 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's 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 with 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 to 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 elderly patients who are non-critically ill 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 from 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 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 with the clinical exam, for the diagnosis of delirium across a range of underlying aetiologies (medication intoxication, hypoxia, electrolyte disturbances and so on), 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 6–24 months following hospital discharge (indicative of non-specific 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 standardised (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 hypothesise 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 (eg, 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 hypothesise that survivors of critical illness with cognitive dysfunction will have a greater proportion of low frequency versus high frequency cortical electrophysiological activity compared with 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 among 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 (eg, APOE and sleep fragmentation interaction) effects on cognitive function. Finally, 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.
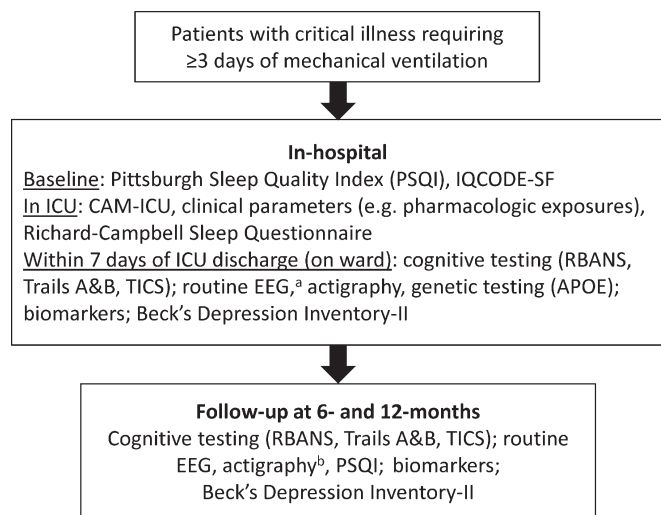
METHODS AND ANALYSIS
Study protocol
This is a multisite, prospective, observational cohort study involving five teaching hospitals (Toronto Western Hospital, Toronto General Hospital, St. Michael's Hospital, Mount Sinai Hospital and Sunnybrook Health Sciences Centre) at the University of Toronto. Study 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 online supplementary file 1). Patients will leave the cohort 1 year after discharge from ICU or at the time of death.

At the time of enrolment, we will record the following data: baseline demographic, admission diagnosis and dates, severity of illness (APACHE II); 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); ICU and hospital length of stay (LOS).

Study personnel blinded to study hypothesis will prospectively collect data on important confounders such as haemodynamic and ventilator parameters, glycaemic control and the presence or absence of delirium on a daily basis. At the time of study enrolment, 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

Table 1	Inclusion and exclusion criteria
Inclusion criteria	► ≥16 years of age
	► Admission to study intensive care unit for invasive mechanical ventilation (≥3 days)
Exclusion criteria	► Advanced cognitive impairment or unable to follow simple commands before their acute illness (eg, end-stage Alzheimer's disease)
	► Primary neurological injury (eg, anoxic injury, stroke or traumatic brain injury)
	► Anticipated death within 3 months of discharge (eg, palliative)
	► Uncontrolled psychiatric illness at hospital admission
	► Not fluent in English
	► Unlikely to adhere with follow-up (eg, no fixed address)
	► Residence greater than 300 km from referral centre

```
┌─────────────────────────────────────────┐
│ Patients with critical illness requiring │
│      ≥3 days of mechanical ventilation   │
└─────────────────────────────────────────┘
                    │
                    ▼
┌─────────────────────────────────────────┐
│               In-hospital                │
│ Baseline: Pittsburgh Sleep Quality       │
│ Index (PSQI), IQCODE-SF                   │
│ In ICU: CAM-ICU, clinical parameters     │
│ (e.g. pharmacologic exposures),          │
│ Richard-Campbell Sleep Questionnaire     │
│ Within 7 days of ICU discharge (on ward):│
│ cognitive testing (RBANS, Trails A&B,    │
│ TICS); routine EEG,ᵃ actigraphy, genetic │
│ testing (APOE); biomarkers; Beck's       │
│ Depression Inventory-II                  │
└─────────────────────────────────────────┘
                    │
                    ▼
┌─────────────────────────────────────────┐
│      Follow-up at 6- and 12-months       │
│ Cognitive testing (RBANS, Trails A&B,    │
│ TICS); routine EEG, actigraphyᵇ, PSQI;   │
│ biomarkers; Beck's Depression            │
│ Inventory-II                             │
└─────────────────────────────────────────┘
```

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

Figure 1 Flow diagram of the COGnitive Outcome and WELLness in survivors of critical illness (COGWELL) study. APOE, Apolipoprotein E; CAM-ICU, Confusion Assessment Method in the ICU; EEG, electroencephalography; ICU, intensive care unit; IQCODE-SF, Informant Questionnaire on Cognitive Decline in the Elderly Short Form; PSQI, Pittsburgh Sleep Quality Index; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; TICS, Telephone Interview for Cognitive Status.

disease(s) present at the time of ICU admission captured by the Charlson and Elixhauser Comorbidity Scales and pre-existing 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, Sequential Organ Failure Assessment Score and APACHE II score; mean PaO_2 of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2), mean arterial pressure and blood glucose, daily mean Riker's sedation agitation score, Confusion Assessment Method in the ICU status and average daily doses of the following medications: benzodiazepines, propofol, narcotics and dexmedetomidine. All patients will undergo standardised 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, Oregon, USA) 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 non-dominant 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 prepaid 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 analysed using MATLAB (Mathworks, Natick, Massachusetts, USA). 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 χ^2 periodogram).[41]

Richards-Campbell Sleep Questionnaire (RCSQ)
This is a five-item, visual analogue scale designed to assess the perception of sleep in patients who are critically ill.[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 (PSQI)
The 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 hospitalisation) 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 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, Ontario, Canada; http://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.

Electroencephalography

Within 7 days after ICU discharge, approximately 30 min of EEG activity will be digitally acquired (XLTEK, Oakville, Ontario, Canada) 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 min 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 characterise 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 10 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-adjusted, sex-adjusted and education-adjusted mean T score is 50 (range 0–100), 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-month and 12-month follow-up. It is made of 11 test items: 10 word immediate and delayed recall tests of memory, a serial 7-s 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 min to administer and score. T-scores are based on normative data from 6726 persons.[56] In an effort to minimise loss to follow-up when in-depth neuropsychological testing cannot 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 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 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 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 five events per variable.[59]

Generalised estimating equations models, to take into account the correlation between the three 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 (0.1–0.5). 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 1 SD 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 patients who are critically ill.[60–64] Efforts to minimise 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 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.

Protocol and registration

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

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.

Author affiliations
[1]Department of Medicine (Critical Care Medicine), University of Toronto, University Health Network, Toronto, Canada
[2]Department of Medicine (Neurology), University of Toronto, Sunnybrook Health Sciences Centre, Toronto, Canada
[3]Department of Psychology, University of Toronto, University Health Network, Toronto, Canada
[4]Department of Medicine (Neurology), University of Toronto, University Health Network, Toronto, Canada
[5]Department of Medicine (Critical Care Medicine), University of Toronto, Sunnybrook Health Sciences Centre, Toronto, Canada
[6]Department of Medicine (Critical Care Medicine), University of Toronto, St. Michael's Hospital, Toronto, Canada

Patient consent Detail has been removed from this case description/these case descriptions to ensure anonymity. The editors and reviewers have seen the detailed information available and are satisfied that the information backs up the case the authors are making.

Ethics approval 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).

Provenance and peer review Not commissioned; externally peer reviewed.

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

REFERENCES

1. Hopkins RO, Jackson JC, Wallace C. Neurocognitive impairments in ICU patients with prolonged mechanical ventilation [abstract]. *J Int Neuropsychol Soc* 2005;11:A60.
2. Ambrosino N, Bruletti G, Scala V, *et al*. Cognitive and perceived health status in patient with chronic obstructive pulmonary disease surviving acute on chronic respiratory failure: a controlled study. *Intensive Care Med* 2002;28:170–7.
3. Iwashyna TJ, Ely EW, Smith DM, *et al*. Long-term cognitive impairment and functional disability among survivors of severe sepsis. *JAMA* 2010;304:1787–94.
4. Semmler A, Widmann CN, Okulla T, *et al*. Persistent cognitive impairment, hippocampal atrophy and EEG changes in sepsis survivors. *J Neurol Neurosurg Psychiatry* 2013;84:62–9.
5. Torgersen J, Hole JF, Kvåle R, *et al*. Cognitive impairments after critical illness. *Acta Anaesthesiol Scand* 2011;55:1044–51.
6. Wilcox ME, Brummel NE, Archer K, *et al*. Cognitive dysfunction in ICU patients: risk factors, predictors, and rehabilitation interventions. *Crit Care Med* 2013;41:S81–98.
7. Lim AS, Yu L, Kowgier M, *et al*. Sleep fragmentation modifies the impact of the APOE4 allele on the risk of incident Alzheimer Disease and cognitive decline in older persons (Platform Presentation). *65th annual meeting of the American Academy of Neurology*. San Diego CA, 2013.
8. Lim AS, Yu L, Costa MD, *et al*. Increased fragmentation of rest-activity patterns is associated with a characteristic pattern of cognitive impairment in older individuals. *Sleep* 2012;35:633–40.
9. Lim AS, Saper CB. Sleep, circadian rhythms, and dementia. *Ann Neurol* 2011;70:677–9.
10. Blackwell T, Yaffe K, Ancoli-Israel S, *et al*. Association of sleep characteristics and cognition in older community-dwelling men: the MrOS sleep study. *Sleep* 2011;34:1347–56.
11. Gozal D, Capdevila OS, Kheirandish-Gozal L, *et al*. APOE epsilon 4 allele, cognitive dysfunction, and obstructive sleep apnea in children. *Neurology* 2007;69:243–9.
12. Kang JE, Lim MM, Bateman RJ, *et al*. Amyloid-beta dynamics are regulated by orexin and the sleep-wake cycle. *Science* 2009;326:1005–7.
13. Ju YE, McLeland JS, Toedebusch CD, *et al*. Sleep quality and preclinical Alzheimer disease. *JAMA Neurol* 2013;70:1–7.
14. Bushey D, Tononi G, Cirelli C. Sleep and synaptic homeostasis: structural evidence in Drosophila. *Science* 2011;332:1576–81.
15. Arrigoni E, Lu J, Vetrivelan R, *et al*. Long-term synaptic plasticity is impaired in rats with lesions of the ventrolateral preoptic nucleus. *Eur J Neurosci* 2009;30:2112–20.
16. Mueller AD, Mear RJ, Mistlberger RE. Inhibition of hippocampal neurogenesis by sleep deprivation is independent of circadian disruption and melatonin suppression. *Neuroscience* 2011;193:170–81.
17. Guzman-Marin R, Suntsova N, Methippara M, *et al*. Sleep deprivation suppresses neurogenesis in the adult hippocampus of rats. *Eur J Neurosci* 2005;22:2111–6.
18. Cirelli C, Faraguna U, Tononi G. Changes in brain gene expression after long-term sleep deprivation. *J Neurochem* 2006;98:1632–45.
19. Orwelius L, Nordlund A, Nordlund P, *et al*. Prevalence of sleep disturbances and long-term reduced health-related quality of life after critical care: a prospective multicenter cohort study. *Crit Care* 2008;12:R97.
20. Lee CM, Herridge MS, Gabor JY, *et al*. Chronic sleep disorders in survivors of the acute respiratory distress syndrome. *Intensive Care Med* 2009;35:314–20.
21. Corder EH, Saunders AM, Strittmatter WJ, *et al*. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* 1993;261:921–3.
22. Poirier J, Davignon J, Bouthillier D, *et al*. Apolipoprotein E polymorphism and Alzheimer's disease. *Lancet* 1993;342:697–9.
23. Saunders AM, Strittmatter WJ, Schmechel D, *et al*. Association of apolipoprotein E allele epsilon 4 with late-onset familial and sporadic Alzheimer's disease. *Neurology* 1993;43:1467–72.
24. O'Hara R, Schröder CM, Kraemer HC, *et al*. Nocturnal sleep apnea/hypopnea is associated with lower memory performance in APOE epsilon4 carriers. *Neurology* 2005;65:642–4.
25. Cosentino FI, Bosco P, Drago V, *et al*. The APOE epsilon4 allele increases the risk of impaired spatial working memory in obstructive sleep apnea. *Sleep Med* 2008;9:831–9.
26. Jordan BD, Relkin NR, Ravdin LD, *et al*. Apolipoprotein E epsilon4 associated with chronic traumatic brain injury in boxing. *JAMA* 1997;278:136–40.
27. Hou X, Guo L, Zhan Q, *et al*. Extracorporeal membrane oxygenation for critically ill patients with 2009 influenza A (H1N1)-related acute respiratory distress syndrome: preliminary experience from a single center. *Artif Organs* 2012;36:780–6.
28. Ely EW, Girard TD, Shintani AK, *et al*. Apolipoprotein E4 polymorphism as a genetic predisposition to delirium in critically ill patients. *Crit Care Med* 2007;35:112–7.
29. Pomara N, Willoughby L, Wesnes K, *et al*. Apolipoprotein E epsilon4 allele and lorazepam effects on memory in high-functioning older adults. *Arch Gen Psychiatry* 2005;62:209–16.
30. Pomara N, Bruno D. Lower plasma β-amyloid levels are associated with moderately greater rate of cognitive decline among older people without dementia. *Evid Based Ment Health* 2011;14:41.
31. Woon FL, Dunn CB, Hopkins RO. Predicting cognitive sequelae in survivors of critical illness with cognitive screening tests. *Am J Respir Crit Care Med* 2012;186:333–40.
32. Jacobson SA, Leuchter AF, Walter DO, *et al*. Serial quantitative EEG among elderly subjects with delirium. *Biol Psychiatry* 1993;34:135–40.
33. Young GB, Blume WT, Campbell VM, *et al*. Alpha, theta and alpha-theta coma: a clinical outcome study utilizing serial recordings. *Electroencephalogr Clin Neurophysiol* 1994;91:93–9.
34. Young GB, Bolton CF, Archibald YM, *et al*. The electroencephalogram in sepsis-associated encephalopathy. *J Clin Neurophysiol* 1992;9:145–52.
35. Watson PL, Shintani AK, Tyson R, *et al*. Presence of electroencephalogram burst suppression in sedated, critically ill patients is associated with increased mortality. *Crit Care Med* 2008;36:3171–7.
36. Charlson M, Szatrowski TP, Peterson J, *et al*. Validation of a combined comorbidity index. *J Clin Epidemiol* 1994;47:1245–51.
37. Elixhauser A, Steiner C, Harris DR, *et al*. Comorbidity measures for use with administrative data. *Med Care* 1998;36:8–27.
38. Weiss AR, Johnson NL, Berger NA, *et al*. Validity of activity-based devices to estimate sleep. *J Clin Sleep Med* 2010;6:336–42.
39. Lim AS, Chang AM, Shulman JM, *et al*. A common polymorphism near PER1 and the timing of human behavioral rhythms. *Ann Neurol* 2012;72:324–34.
40. Lim AS, Yu L, Costa MD, *et al*. Quantification of the fragmentation of rest-activity patterns in elderly individuals using a state transition analysis. *Sleep* 2011;34:1569–81.
41. Sokolove PG, Bushell WN. The chi square periodogram: its utility for analysis of circadian rhythms. *J Theor Biol* 1978;72:131–60.
42. Richards KC, O'Sullivan PS, Phillips RL. Measurement of sleep in critically ill patients. *J Nurs Meas* 2000;8:131–44.
43. Buysse DJ, Reynolds CF, Monk TH, *et al*. The Pittsburgh Sleep Quality Index (PSQI): A new instrument for psychiatric research and practice. *Psychiatry Research* 1989;28:193–213.
44. Hinrikus H, Suhhova A, Bachmann M, *et al*. Spectral features of EEG in depression. *Biomed Tech* 2010;55:155–61.
45. Helkala EL, Laulumaa V, Soikkeli R, *et al*. Slow-wave activity in the spectral analysis of the electroencephalogram is associated with cortical dysfunctions in patients with Alzheimer's disease. *Behav Neurosci* 1991;105:409–15.

46. Soininen H, Partanen J, Laulumaa V, *et al*. Longitudinal EEG spectral analysis in early stage of Alzheimer's disease. *Electroencephalogr Clin Neurophysiol* 1989;72:290–7.
47. Richter P, Werner J, Heerlein A, *et al*. On the validity of the Beck Depression Inventory. A review. *Psychopathology* 1998;31:160–8.
48. Duggan MC, Wang L, Wilson JE, *et al*. The relationship between executive dysfunction, depression, and mental health-related quality of life in survivors of critical illness: Results from the BRAIN-ICU investigation. *J Crit Care* 2017;37:72–9.
49. Jorm AF. The Informant Questionnaire on cognitive decline in the elderly (IQCODE): a review. *Int Psychogeriatr* 2004;16:275–93.
50. Randolph C, Tierney MC, Mohr E, *et al*. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): preliminary clinical validity. *J Clin Exp Neuropsychol* 1998;20:310–9.
51. Duff K, Hobson VL, Beglinger LJ, *et al*. Diagnostic accuracy of the RBANS in mild cognitive impairment: limitations on assessing milder impairments. *Arch Clin Neuropsychol* 2010;25:429–41.
52. Duff K, Humphreys Clark JD, O'Bryant SE, *et al*. Utility of the RBANS in detecting cognitive impairment associated with Alzheimer's disease: sensitivity, specificity, and positive and negative predictive powers. *Arch Clin Neuropsychol* 2008;23:603–12.
53. McKay C, Casey JE, Wertheimer J, *et al*. Reliability and validity of the RBANS in a traumatic brain injured sample. *Arch Clin Neuropsychol* 2007;22:91–8.
54. Hobson VL, Hall JR, Humphreys-Clark JD, *et al*. Identifying functional impairment with scores from the repeatable battery for the assessment of neuropsychological status (RBANS). *Int J Geriatr Psychiatry* 2010;25:525–30.
55. Reitan RM, W D. *The Halstead Reitan neuropsychological test battery*. Tucson, AZ: Neuropsychology Press, 1985.
56. Knopman DS, Roberts RO, Geda YE, *et al*. Validation of the telephone interview for cognitive status-modified in subjects with normal cognition, mild cognitive impairment, or dementia. *Neuroepidemiology* 2010;34:34–42.
57. Plassman BL, Langa KM, Fisher GG, *et al*. Prevalence of dementia in the United States: the aging, demographics, and memory study. *Neuroepidemiology* 2007;29(1-2):125–32.
58. Crimmins EM, Kim JK, Langa KM, *et al*. Assessment of cognition using surveys and neuropsychological assessment: the Health and Retirement Study and the Aging, Demographics, and Memory Study. *J Gerontol B Psychol Sci Soc Sci* 2011;66(Suppl 1):i162–i171.
59. Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and Cox regression. *Am J Epidemiol* 2007;165:710–8.
60. Davidson TA, Rubenfeld GD, Caldwell ES, *et al*. The effect of acute respiratory distress syndrome on long-term survival. *Am J Respir Crit Care Med* 1999;160:1838–42.
61. Herridge MS, Tansey CM, Matté A, *et al*. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med* 2011;364:1293–304.
62. Girard TD, Kress JP, Fuchs BD, *et al*. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet* 2008;371:126–34.
63. Alexander LD, Pettersen JA, Hopyan JJ, *et al*. Long-term prediction of functional outcome after stroke using the Alberta Stroke Program Early Computed Tomography Score in the subacute stage. *J Stroke Cerebrovasc Dis* 2012;21:737–44.
64. Clarke PJ, Lawrence JM, Black SE. Changes in quality of life over the first year after stroke: findings from the Sunnybrook Stroke Study. *J Stroke Cerebrovasc Dis* 2000;9:121–7.
65. Tansey CM, Matté AL, Needham D, *et al*. Review of retention strategies in longitudinal studies and application to follow-up of ICU survivors. *Intensive Care Med* 2007;33:2051–7.