ABSTRACT

Introduction Delirium is a major public health issue for surgical patients and their families because it is associated with increased mortality, cognitive and functional decline, prolonged hospital admission and increased healthcare expenditures. Based on preliminary data, this trial tests the hypothesis that intravenous caffeine, given postoperatively, will reduce the incidence of delirium in older adults after major non-cardiac surgery.

Methods and analysis The CAFFEINE, Postoperative Delirium And Change In Outcomes after Surgery-2 (CAPACHINOS-2) Trial is a single-centre, placebo-controlled, randomised clinical trial that will be conducted at Michigan Medicine. The trial will be quadruple-blinded, with clinicians, researchers, participants and analysts all masked to the intervention. The goal is to enrol 250 patients with a 1:1:1:1 allocation ratio: dextrose 5% in water placebo, caffeine 1.5 mg/kg and caffeine 3 mg/kg as a caffeine citrate infusion. The study drug will be administered intravenously during surgical closure and on the first two postoperative mornings. The primary outcome will be delirium, assessed via long-form Confusion Assessment Method. Secondary outcomes will include delirium severity, delirium duration, patient-reported outcomes and opioid consumption patterns. A substudy analysis will also be conducted with high-density electroencephalography (72-channel system) to identify neural abnormalities associated with delirium and Mild Cognitive Impairment at preoperative baseline.

Ethics and dissemination This study was approved by the University of Michigan Medical School Institutional Review Board (HUM00218290). An independent data and safety monitoring board has also been empanelled and has approved the clinical trial protocol and related documents. Trial methodology and results will be disseminated via clinical and scientific journals along with social and news media.

Trial registration number NCT05574400.

INTRODUCTION

Delirium is a syndrome characterised by failure of basic cognitive functions and affects approximately 20%–50% of older surgical patients.1,2 Delirium during surgical recovery is associated with increased mortality,3 cognitive and functional decline,4,5 and prolonged hospitalisation.6 In fact, 3-year survival rates for acutely hospitalised patients with delirium and sub syndromal delirium are both less than 50%.7 Delirium also creates a substantial economic burden, with total healthcare cost estimates ranging from US$38 to US$152 billion annually.8 Older age is predictive of delirium after surgery,9-11 and with aging surgical populations, the incidence of postoperative delirium and related complications are likely to increase in the coming years.

Caffeine represents a novel, neurobiologically informed candidate intervention for preventing postoperative delirium. Caffeine promotes arousal and improves cognitive function by facilitating information processing.12-14 Moreover, human volunteer studies have demonstrated that caffeine accelerates emergence from anaesthesia and allows for earlier psychomotor testing after general anaesthesia.15 In a small single-centre trial, caffeine also reduced the prevalence of postanaesthesia care unit (PACU) delirium.16 This was, however, a post hoc...
analysis. Substudy analyses from this trial also revealed that caffeine improves cortical dynamics supporting cognition. These findings have not yet been corroborated by other perioperative clinical trials, as prior trials have not focused on delirium as the primary outcome. In fact, many of these trials did not include any cognitive outcomes (table 1).

The objective of this trial is to test the effects of caffeine on postoperative cognitive and clinical recovery. Specifically, this study tests the primary hypothesis that caffeine will reduce the incidence of postoperative delirium. The secondary objectives are to (1) test whether caffeine positively impacts the quality of postoperative recovery and (2) identify neural abnormalities associated with delirium and mild cognitive impairment via advanced electroencephalographic (EEG) analysis.

METHODS AND ANALYSIS
Trial overview and design
The Caffeine, Postoperative Delirium And CHange IN Outcomes after Surgery (CAPACHINOS)-2 Trial is a randomised, placebo-controlled clinical trial conducted at Michigan Medicine. The trial has been approved by the University of Michigan Medical School Institutional Review Board (HUM00218290), and written consent will be obtained from all trial participants. Additional consent provisions will also be provided for data sharing and future research. The trial was registered on ClinicalTrials.gov (NCT05574400, 10 October 2022, principal investigator (PI): PEV) and the complete trial protocol is available in online supplemental appendix 1. CAPACHINOS-2 also meets criteria put forth by the Standard Protocol Items for Randomised Trials (online supplemental appendices 2 and 3 for written informed consent document). Any required protocol amendments will be communicated to the University of Michigan Medical School Institutional Review Board, National Institute on Aging and data and safety monitoring board (DSMB). Amendments will also be logged in the full clinical trial protocol (online supplemental appendix 1).

The trial will follow a parallel arm design, with a 1:1:1 allocation ratio (placebo: 1.5 mg/kg caffeine; 3 mg/kg caffeine) (figure 1). Participants will be block-randomised, and randomisation will also be stratified by age (70–74 vs ≥75 years of age) and sex. The randomisation scheme was developed by the study statistician team (GM and EJ), and the randomisation schedule will be managed by the hospital research pharmacy. The study will follow a quadruple-blinded design: participants, researchers, clinicians and analysts will be blinded to the intervention.

Eligibility criteria
Patients ≥70 years of age presenting for major noncardiac, non-intracranial, non-major vascular (eg, operations above the diaphragm) surgery with anticipated hospital length of stay at least 48 hours will be eligible for the trial. Exclusion criteria include the following: emergency surgery, outpatient surgery, severe cognitive impairment precluding capacity for informed consent, seizure disorder history, intolerance or allergy to caffeine, weight >130 kg (as a 3 mg/kg dose would approach the upper limit of daily intake recommended by the Food and Drug Administration), enrolment in a conflicting study, acute hepatic failure (inadequate caffeine metabolism), acute kidney injury preoperatively (which may impair caffeine clearance), diagnosis of pheochromocytoma (to avoid unsafe increases in blood pressure), severe audiovisual...
Impairment preventing participation in cognitive function testing and non-English speaking.

**Interventions**
Participants will be block randomised with a 1:1:1 allocation ratio (placebo: 1.5 mg/kg caffeine: 3 mg/kg caffeine) in a three-arm parallel design as previously described. Prepared intravenous syringe solutions of dextrose 5% in water (D5W) placebo or caffeine citrate will be directly delivered to the operating room prior to the surgery of enrolled participants. For the next two postoperative mornings, the study drug will be given with scheduled, morning medications between approximately 8:30–9:30 hours as administered and overseen by a research team nurse.

Each dose was chosen based on preliminary data and literature review. First, the lower dose (1.5 mg/kg, approximately one cup of coffee) might lower the risk of adverse side effects (eg, nausea, vomiting, anxiety). Second, reduced dosing may also be appropriate for older populations, as the cognitive effects of caffeine may be more pronounced with age. Serum caffeine concentration also increases with age, as the total volume of caffeine distribution is reduced in older patients. As such, higher peak serum caffeine concentrations are observed with advancing age after both intravenous and oral administration. The higher dose of 3 mg/kg (approximately two cups of coffee) might provide added cognitive benefit. In fact, the mean weight-based dose for participants receiving caffeine and not experiencing any delirium in our preliminary trial was 3 mg/kg. Additional cognitive benefit has also been observed with this dose, particularly for domains relevant to delirium (eg, attention, vigilance) and after sleep deprivation, which is commonly experienced in the hospital setting.

**Figure 1** Consolidated Standards of Reporting Trials flow diagram presented. The design is a three-arm parallel design with a 1:1:1 allocation ratio (placebo: low-dose caffeine: high-dose caffeine). D5W, dextrose 5% in water; EEG, electroencephalography.
Nonetheless, this higher dose may also be associated with additional side effects (e.g., anxiety, gastrointestinal distress, nausea/vomiting), so multiple dosing arms will help determine optimal dosing to maximise benefit-to-risk ratios.

The study drug will be administered as an intravenous infusion, using an infusion pump, over 30 (±5) min at three time points: (1) the beginning of surgical closure during the operation, (2) first postoperative morning and (3) second postoperative morning. The lower dose will consist of 1.5 mg/kg caffeine base, and higher dose will contain 3 mg/kg caffeine base; both caffeine drugs will be dissolved in 40 mL of D5W. No dose or timing changes are anticipated, and the infusion will be administered over the entire 30 (±5) min. A research team nurse will oversee the drug administration and monitor blood pressure (every 5 min), heart rate, heart rhythm (via five-lead electrocardiography), and continuous pulse oximetry for the full 30 min infusion. This monitoring will continue for 10 min after the infusion, then monitoring will continue per standard clinical protocols for each hospital unit. The study drug will be prepared, handled, and stored per standard hospital pharmacy protocols as described in the complete trial protocol (see online supplemental appendix 1). Clinical teams will be notified of any adverse drug reactions, and the infusion will be stopped for any concerns or adverse events suspected in relation to the drug infusion.

Outcomes

Timing of outcomes is presented in figure 2, which illustrates participant flow through the trial. The primary outcome is delirium, rated using the long-form Confusion Assessment Method (CAM). The CAM will be rated based on a brief cognitive screen that includes testing of sustained attention, short-term recall, orientation and the Delirium Symptom Interview as previously described. Signs of acute change as reported by family members, care partners and/or clinicians will also be incorporated into the CAM ratings. This cognitive testing and CAM rating will occur at preoperative baseline, 1 hour after PACU admission, and twice daily for the first three postoperative days. A daily chart review method will be performed to complement CAM screening, which will be particularly useful if in-person CAM screening is not possible for a given day. Research team members will undergo formal CAM training, which will entail video training (available via American Geriatrics Society CoCare website: https://help.agscocare.org) and educational sessions with PEV and AM, as our team has used this training programme.

Figure 2  Participant flow through the trial is illustrated. Baseline clinical and cognitive assessments will take place during preoperative enrolment. Whole-scalp, wireless, high-density (72-channel) electroencephalography (EEG) recordings will take place immediately prior to surgery, intraoperatively and during the early stages of postanaesthesia care unit (PACU) recovery. A low-resolution four-channel system will then be used for recordings during drug infusion on the subsequent mornings. The study drug will be given during surgical closure and again during the first two postoperative mornings. A follow-up survey will then be conducted 30 days after discharge. AD8, Eight-item Informant Interview to Differentiate Ageing and Dementia; CAM, Confusion Assessment Method; IADL, Independent Activities of Daily Living; MoCA, Montreal Cognitive Assessment; PONV, Postoperative Nausea and Vomiting; PROMIS, Patient-Reported Outcomes Measurement Information System; QoR, Quality of Recovery; RASS, Richmond Agitation Sedation Scale; VAS, Visual Analogue Scale; AM, Ante Meridiem; PM, Post Meridiem.
for previous trials. After this initial training, trainees will then accompany fully trained team members during CAM interviews, and trainees will independently conduct their own CAM assessment. Trainees will need to achieve agreement on final CAM scores (ie, delirium or no delirium) for two non-delirious and two delirious participants before independently assessing trial participants with the CAM. Group inter-rater reliability assessment will then be tested every 6 months using previously described methods.

### Secondary and exploratory outcomes

Secondary outcomes are presented in table 2. These outcomes relate to both delirium (eg, delirium severity, delirium duration) and patient-reported quality of recovery. Given the effects of caffeine on perioperative headache, pain and opioid consumption, these endpoints will also be tested and reported. Exploratory outcomes will include anaesthetic emergence time (time from surgical closure finish to extubation), postoperative pulmonary complications (eg, reintubation), hospital length of stay, discharge disposition and 30-day Montreal Cognitive Assessment and Patient-Reported Outcomes Information Measurement System Physical Function 10a scores. Additional exploratory and safety outcomes are included in online supplemental appendix 1.

### Control variables and other assessments

Daily caffeine intake (number of daily beverages, n) will be assessed among participants. Baseline function will also be evaluated via preoperative Eight-Item Informant Interview to Differentiate Aging and Dementia (AD8), Montreal Cognitive Assessment and Instrumental Activities of Daily Living. Nausea and vomiting will be assessed via the Postoperative Nausea and Vomiting Intensity Scale in the PACU and on the first two postoperative afternoons. Baseline variables and other confounders will be incorporated into statistical models as outlined below (see the Statistical analysis section).

### Data management

Data collection will be the responsibility of the clinical trial staff under the supervision of the study PI (PEV). Research data will initially be reported on paper case...
report forms during patient interactions, and these deidentified data will be uploaded to the Research Electronic Data Capture (REDCap) application. This is an electronic database that resides on a secured, password-protected network managed by the Michigan Institute for Clinical and Health Research (National Institutes of Health-funded Clinical and Translational Science Awards institute of the University of Michigan). Quality control procedures will also be implemented beginning with the data entry system, and data quality checks will be generated. The Michigan Institute for Clinical and Health Research also performs routine, scheduled maintenance and quality control checks on the REDCap system. The REDCap system also incorporates logic that requires appropriate responses and missing/incorrect data are readily and transparently highlighted. We will also request independent audits by the Michigan Institute for Clinical & Health Research during trial operations.

### Statistical analysis

Descriptive statistics will initially be calculated, with categorical outcomes presented as proportions (frequencies) and continuous data presented as means (±SD) or medians (IQR). Normality of distribution will be assessed using the Shapiro-Wilk test, and parametric or non-parametric tests will be applied as appropriate.

As mentioned previously, postoperative delirium will serve as the primary endpoint as assessed through the first three postoperative days as previously described. The primary analytical test will be a multivariable logistic regression model that will follow the generalised estimating equations (GEEs) approach. Independent variables will include the placebo group (reference), 1.5 mg/kg caffeine group, 3 mg/kg caffeine group, baseline caffeine intake and a priori variables that may independently predict delirium (eg, age, male sex, American Society of Anesthesiologists Physical Status score, baseline cognitive function via Montreal Cognitive Assessment, baseline functional status via Instrumental Activities of Daily Living, depression and epidural use). Baseline cohort imbalances, defined by absolute standardised differences >0.20, will also be included in this model. Missing delirium data will be assessed for randomness using the Little’s Missing Completely at Random Test. If data are missing at random, imputation will be performed, and these results will be compared with results with the actual data in a supplementary appendix. If data are not missing at random, no imputation will be performed, and the Cochrane-Armitage test will be used to assess for the proportion of missing data across each arm.

For secondary endpoints, a similar GEE-based approach will be used. Within-group and between-group comparisons will be analysed based on coefficients in the model. This approach also allows for flexibility with missing data. Unstandardised beta coefficients will be presented with 95% CIs and p values (<0.05 will be considered statistically significant). All GEE models will use the empirical parameter estimates with an exchangeable correlation matrix.

As indicated previously, models will adjust for baseline cohort imbalances. Additionally, for Quality of Recovery and headache severity, the differential effect of habitual caffeine consumption and group will be tested. This will be tested via interaction term of habitual caffeine consumption with caffeine group (placebo, 1.5 mg/kg caffeine, 3 mg/kg caffeine). The daily number of caffeinated beverages will be recorded for each participant, and the resulting distribution will be analysed and used to inform the most appropriate categorisation of habitual caffeine users (eg, non-users, low use, high use).

### Sample size and power calculations

Sample size calculations were conducted via GEE Tests for Multiple Proportions in a Cluster-Randomised Design with Power Analysis and Sample Size Software (2022; NCSS). Significance level (α) was set at 0.05. A post-operative delirium incidence (including the PACU time frame) of 30% was conservatively estimated based on our preliminary trial. A sample size of 250 participants will provide between 80% and 95% power assuming a control group delirium incidence of 30%, 10–50% in the 1.5 mg/kg group and 10%–15% in the 3 mg/kg group. These effect sizes are estimated from our preliminary trial data with a similar dosing range (1.7–4.5 mg/kg; median dose 2.5 mg/kg) and absolute risk reduction >20%. Increased potency may be expected with older patients given the reduced pharmacologic volume of distribution and a possible age-caffeine interaction effect with respect to cognition. This sample size also accounts for an approximate 10% dropout rate. Lastly, no interim analyses are planned in relation to the primary outcome.

### Prespecified substudy and subgroup analyses

A substudy analysis will be conducted to identify cortical dynamics associated with postoperative delirium. Based on our preliminary data, we hypothesise that delirium will reflect deviations in neural criticality, which is a postulated state of a system that is poised at the boundary of a phase transition. Proximity to neural state transitions may allow dynamic, flexible shifts in neural processes for supporting cognitive function. In our preliminary single-centre trial (CAPACHINOS-1), surrogate EEG measures of neural criticality were reduced with PACU delirium and increased with caffeine. As such we also hypothesise that caffeine will restore critical dynamics (ie, proximity to criticality) concurrent with reduced delirium risk. To test these hypotheses, a wireless, whole-scalp, high-density (72-channel) system (Mobile-72, CGX, San Diego, California, USA) will be used in the immediate perioperative setting (and intraoperatively). This whole-scalp, high-density system will also enable analysis of functional connectivity patterns and neuroanatomical source analyses in relation to delirium and cognitive function.

A trial subgroup analysis will also be conducted in patients meeting criteria for mild cognitive impairment at preoperative baseline (anticipated n=50) based on preoperative AD8 screening, Montreal Cognitive...
Institute for Clinical and Health Research to improve recruitment diver-
caffeine administration is not associated with major adverse cardio-
disease. Caffeine is one of the most widely studied drugs worldwide,
Cognitive Impairment, syndrome that may predict future Alzheimer’s
delirium and related complications9; as such, this trial specifically
Patients 70 years of age and older have relatively high risk of postoper-
inpatient admission and meeting all eligibility criteria will be eligible.

Outcome after Surgery—

What is the clinical, scientific or social value that will be gained from
The candidate intervention being tested, caffeine, may improve health
and/or well-being for older, hospitalised patients. Specifically, caffeine
may reduce the risk of delirium after surgery, which would prevent an
otherwise distressing experience for patients and family members.
Moreover, caffeine may also reduce the risk of downstream complica-
tions, such as prolonged hospitalisation, falls and additional cognitive or
functional decline.

1. What is the clinical, scientific or social value that will be gained from
the proposed research?

2. Will the proposed research be conducted in a scientifically rigorous
manner, including accepted scientific methods, principles and reliable
practices?

Multiple strategies will be incorporated to enhance methodological
rigour for producing reliable, valid results. First, this will be a ran-
domised, placebo-controlled trial. Stratified, block-randomisation
will be used to mitigate selection bias and balance prognostically
relevant variables to delirium. The trial will also follow a quadruple-
blinded design: participants, research teams, clinical teams and
analysts will all be blinded to intervention allocation, even during the
analysis phase. Robust modelling strategies will also be used that
account for missing data and incorporate relevant confounders.
External audits will also be performed via the Michigan Institute for
Clinical and Health Research, which will help track and minimise
deviations from the trial protocol and manual. Lastly, a data and
safety monitoring board (DSMB) has been established to monitor
study progress, safety outcomes and adverse events. These ad-
ditional monitoring strategies will strengthen rigour of trial opera-
tions and provide additional layers of independent oversight.

3. Are participants selected in a fair manner, such that stigmatised and
vulnerable individuals are not targeted for risky research?

All participants presenting for major non-cardiac surgery requiring
inpatient admission and meeting all eligibility criteria will be eligible.
Patients 70 years of age and older have relatively high risk of postoper-
ative delirium and related complications8; as such, this trial specifically
aims to test an intervention in this vulnerable population for improving
health outcomes. Lastly, the trial team is also working with the Michigan
Institute for Clinical and Health Research to improve recruitment diver-
sity, equity and inclusion efforts.

4. Is there a favourable benefit: risk ratio, such that the risks are ac-
ceptably proportionate to the benefits to participants and society more
broadly?

As previously outlined, caffeine may offer a direct benefit to participants
by reducing the risk of delirium and related complications. If found to
be effective, caffeine could then also be offered to future patients and
tested in broader clinical settings. Future patients could also benefit by
the advanced neurophysiological analysis that will be conducted, which
will help to identify neurobiological underpinning of delirium and Mild
Cognitive Impairment, syndrome that may predict future Alzheimer’s
disease. Caffeine is one of the most widely studied drugs worldwide,
and the weight of available, relevant evidence suggests that acute
caffeine administration is not associated with major adverse cardio-
vascular perturbations or other untoward events,22 44–46 particularly at
moderate doses consistent with those chosen for this trial. A full de-
scription of anticipated benefits and risks is available in the full trial
protocol (online supplemental appendix 1).

5. Will independent reviews take place, such that a committee, with an
appropriate range of expertise, will have the ability to approve, amend
or terminate the study?

The trial has been approved by the University of Michigan Medical
School Institutional Review Board, who will monitor study progress and
outcomes, including adverse events, throughout the trial lifespan.
As mentioned above, an independent DSMB has also been established

Box 1 CAffeeine, Postoperative Delirium And CHange In
Outcomes after Surgery—

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and/or well-being for older, hospitalised patients. Specifically, caffeine
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Box 1 Continued

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School Institutional Review Board, who will monitor study progress and
outcomes, including adverse events, throughout the trial lifespan.
As mentioned above, an independent DSMB has also been established

6. Will informed consent be obtained from all trial participants?

Written informed consent will be obtained from all participants prior to
trial enrolment. The written informed consent document was re-
viewed and approved by both the University of Michigan Medical School
Institutional Review Board and DSMB. This document also meets re-
quirements outlined in the US Department of Health and Human

7. Does the proposed study engender respect for potential and enrolled
participants?

All potential and enrolled participants will be treated with respect,
and patient autonomy will be respected throughout the trial and hos-
pital lifespans. Privacy will be ensured by managing Protected Health
Information through secure, confidential procedures outlined in the pro-
tocol. Participants will be free to withdraw from the trial at any time
without repercussions or untoward consequences. If new information
is obtained during trial enrolment that may impact risk to a participant,
this information will be promptly relayed and informed consents will be
updated as required. Participants will be closely monitored during the
study as outlined in the protocol, and links www.ClinicalTrials.gov reg-
istry entry will be provided, such that participants will be able to review
study information and results.

Data and safety monitoring

All trial participants will be monitored by both the research staff—including direct PI oversight—and clinical
teams based on standard hospital care and protocols. The research team will monitor patients daily for adverse
events, which will be reported based on IRB and NIA guidelines. A licensed research nurse will also monitor partic-
pants during caffeine infusions (see full trial protocol, online supplemental appendix 1, for complete details).
Additionally, a DSMB has been empanelled to act in an advisory capacity to the NIA and periodically evaluate the

progress and safety of the study. Members of the DSMB have appropriate (and complementary) expertise that is suited for the trial, and each member has confirmed no conflict of interest via signed statement submitted to the NIA. The DSMB will thus be able to make independent, impartial recommendations to the NIA throughout the trial lifespan. Complete DSMB details are available in the full trial protocol (online supplemental appendix 1).

**Patient and public involvement**
None.

**Trial strengths and limitations**
Notable strengths of this study merit consideration. This is a placebo-controlled trial, and the stratified, block-randomised design will alleviate trial arm imbalance and mitigate selection bias. Multiple doses will be tested, which will help to determine the optimal dosing threshold. To enhance trial rigour, we will follow a quadruple-blinded design; team statisticians will perform analyses in a blinded manner, and the blind will only be lifted after analysis of the primary and secondary outcomes is complete. The DSMB and independent auditing services will also provide additional monitoring support. The advanced EEG analysis will also help to identify cortical dynamics underlying both delirium and caffeine administration, which will advance neurobiological understanding of delirium and cognitive function.

Important limitations also warrant consideration. Trial generalisability will be limited, given the focus on older patients and single-centre design of the study. Additionally, although different doses will be tested, it is possible that a more sophisticated, personalised or dynamic caffeine dosing strategy is required to optimise postoperative neurocognitive and clinical recovery. For example, relatively higher doses may be required for cognitive benefit in the early postoperative setting with residual anaesthesia or in those with high levels of habitual use. A future adaptive trial may also be warranted, particularly when a more comprehensive understanding of perioperative benefits and risks of caffeine are known, as well as the optimal timing of caffeine administration. While this trial will not provide definitive answers to these questions, the study will serve as an initial step because it tests different caffeine doses along multiple time points of postoperative recovery in older adults.

**Ethics and dissemination**
Derived from landmark declarations, codes and guidelines, Emanuel et al propose seven requirements for systematically analysing the ethical framework of a proposed clinical research study. These requirements are the following: social or scientific value, scientific validity, fair participant selection, favourable benefit: risk ratio, independent review, informed consent, and respect for potential and enrolled participants. This framework is applied to the current trial, with considerations outlined in box 1. As mentioned previously, the trial was also approved by the University of Michigan Medical School Institutional Review Board (HUM00218290), and written informed consent will be obtained from all participants. An expanded discussion of risks and benefits is also included in the full clinical trial protocol (online supplemental appendix 1).

This trial will be presented at academic medical conferences, and trial operations and results will be disseminated via social and news media. As noted, the trial has been registered at www.ClinicalTrials.gov (NCT05574400), and updates will be made publicly available on this website. On trial completion, results will be published in medical and scientific journals.

**Contributors** The study design was conceptualised by PEV, JR, GV and GAM. PEV drafted the initial manuscript. GM and EJ created the statistical analysis plan. AM, NR, SM and UL created the data acquisition and management plan. EMS and SKI contributed to the delirium training and assessment plan, in addition to trial protocol development more broadly. Lastly, all authors contributed to the manuscript writing, critically reviewed the manuscript for intellectual content and approved the final manuscript.

**Funding** Funding provided by the US National Institutes of Health (PEV, R01AG075005).

**Competing interests** PEV and AM receive support from Blue Cross Blue Shield of Michigan for quality improvement work related to delirium (but unrelated to this current study).

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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