


BMJ Open Caffeine, Postoperative Delirium And Change In Outcomes after Surgery (CAPACHINOS)-2: protocol for a randomised controlled trial

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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 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

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Randomised, placebo-controlled clinical trial to test the effects of caffeine on postoperative cognitive and clinical recovery in older adults.
- ⇒ The trial will be quadruple-blinded: clinicians, participants, researchers and analysts will be blinded to intervention allocation.
- ⇒ An independent data and safety monitoring board will monitor study operations.
- ⇒ High-density electroencephalography will be used to identify neural processes associated with delirium and related neurocognitive disorders.
- ⇒ The single-centre nature of the trial may limit generalisability.

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 subsyndromal 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

**Table 1** Perioperative caffeine trials

Study	Description	Primary outcome	Cognitive outcomes
Hampel <i>et al</i> 1995 ¹⁸	Small clinical trial of habitual caffeine users (n=40). Caffeine administration on the day of surgery reduced postoperative headache risk.	Postoperative headache	▶ None
Weber <i>et al</i> 1997 ¹⁹	Prophylactic intravenous caffeine reduced risk of postoperative headache in surgical outpatients (n=234) with headache risk factors.	Postoperative headache	▶ None
Gouda 2010 ²⁰	Time to eye opening, extubation and response to commands were reduced in patients with obstructive sleep apnoea randomised to caffeine (n=30).	Not specified	▶ Time to eye opening and response to commands with anaesthetic emergence
Steinbrook <i>et al</i> 2013 ²¹	Nausea was more common in participants randomised to caffeine (16/62, 26%) compared with placebo (7/69, 10%).	Postoperative nausea and vomiting	▶ None
Lagier <i>et al</i> 2018 ²²	Caffeine was not associated with a reduced risk of new postoperative atrial fibrillation (n=110 participants).	Postoperative atrial fibrillation	▶ None
Liu <i>et al</i> 2021 ²³	Postoperative caffeinated green tea administration (n=40) was associated with reduced time to return of gastrointestinal function compared with placebo (n=40).	Time to postoperative recovery of gastrointestinal function	▶ None
Vlisides <i>et al</i> 2021 ¹⁶	Intravenous caffeine, administered intraoperatively (n=30), did not reduce postoperative opioid consumption compared with placebo (n=30).	Postoperative opioid consumption	▶ Postoperative delirium (PACU through postoperative day three) ▶ Executive function—trail making test

PACU, postanesthesia care unit.

analysis. Substudy analyses from this trial also revealed that caffeine improves cortical dynamics supporting cognition.¹⁷ 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).^{16 18–23}

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 via validated patient-reported measures 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 non-cardiac, 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

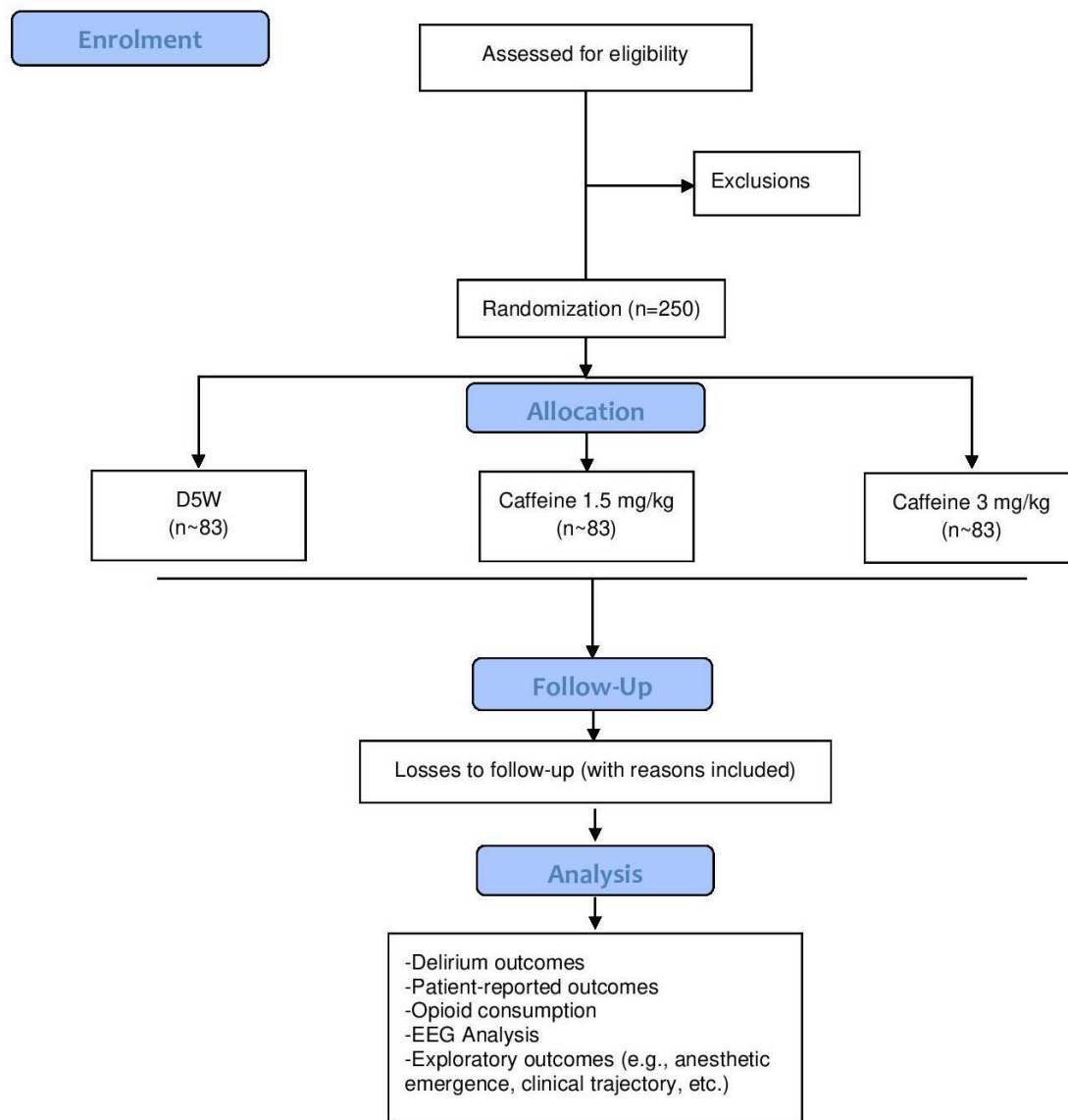


Figure 1 Consolidated Standards of Reporting Trials flow diagram presented. The design is a three-arm parallel design with a 1:1:1 allocation ratio (placebo: low-dose caffeine: high-dose caffeine). D5W, dextrose 5% in water; EEG, electroencephalography.

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 coffee²⁴) might lower the risk

of adverse side effects (eg, nausea, vomiting, anxiety).²² Second, reduced dosing may also be appropriate for older populations, as the cognitive effects of caffeine may be more pronounced with age.²⁵ Serum caffeine concentration also increases with age, as the total volume of caffeine distribution is reduced in older patients.²⁶ As such, higher peak serum caffeine concentrations are observed with advancing age after both intravenous and oral administration.²⁶ The higher dose of 3 mg/kg (approximately two cups of coffee²⁴) might provide added cognitive benefit.²⁷ In fact, the mean weight-based dose for participants receiving caffeine and not experiencing any delirium in our preliminary trial was 3 mg/kg.¹⁶ Additive cognitive benefit has also been observed with this dose, particularly for domains relevant to delirium (eg, attention, vigilance)^{28–31} and after sleep deprivation,³² which is commonly experienced in the hospital setting.

Nonetheless, this higher dose may also be associated with additional side effects (eg, 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 (\pm 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 (\pm 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).³³ 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.^{34–36}

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,³⁷ 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

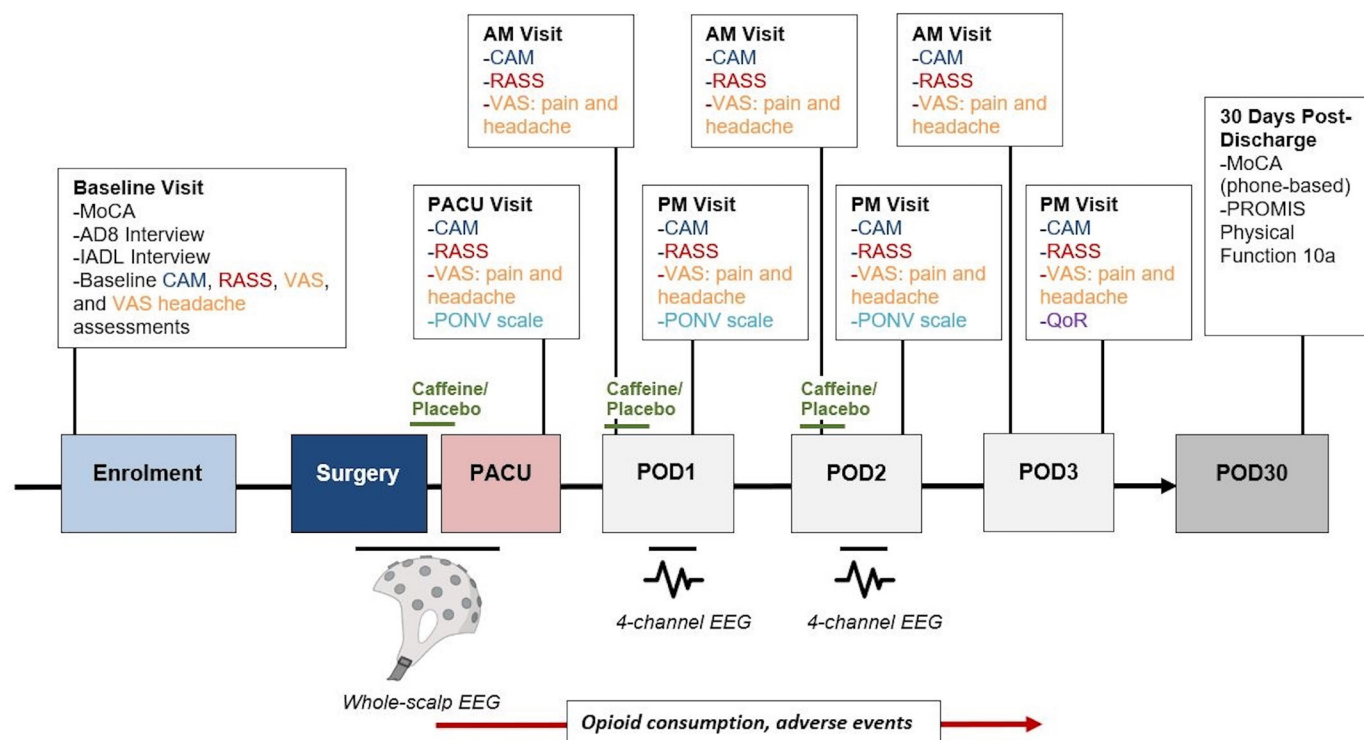


Figure 2 Participant flow through the trial is illustrated. Baseline clinical and cognitive assessments will take place during preoperative enrolment. Whole-scalp, wireless, high-density (72-channel) electroencephalography (EEG) recordings will take place immediately prior to surgery, intraoperatively 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.

Table 2 Primary and secondary trial outcomes

Outcomes	Endpoint	Justification for endpoint
Primary outcome		
Delirium	Long-form Confusion Assessment Method (CAM), scored based on brief cognitive screening tests, obtained 1 hour after PACU admission and twice daily for the first three postoperative days. The CAM will be complemented by a validated chart review method ^{37 53} to mitigate missing delirium assessments.	The CAM is the most widely used measure for identification of delirium worldwide, validated in >22 studies with sensitivity and specificity of >90% ^{33 54 55}
Secondary outcomes		
Delirium severity	Measured via the same long-form CAM (CAM-S score). ⁵⁶	CAM-S is a continuous scoring metric based on the long-form CAM (scored 0–19, 19=highest severity). The CAM-S demonstrates high inter-rater reliability (0.88–0.92) and strong correlation with important clinical outcomes, including hospital length of stay, cognitive and functional decline, discharge disposition and mortality. ⁵⁶
Delirium duration	Measured by the cumulative no of days (n) with a positive delirium screen.	Delirium duration is associated with poor hospital outcomes. ⁵⁷
Quality of recovery	Patient-reported 15-item Quality of Recovery score, ⁵⁸ which will be assessed in the afternoon on postoperative day three.	The original Quality of Recovery ⁵⁹ scale has been used for 20 years in perioperative clinical trials research. Extensive validity, ⁶⁰ reliability ⁶⁰ and minimal clinically important difference data ⁶¹ have been published. This scale was also recently endorsed by the Standardised Endpoints in Perioperative Medicine Initiative. ⁶² Caffeine is postulated to ameliorate pain and postoperative confusion, which are each independently associated with poor recovery on this scale. ⁶³
Sedation and agitation	Sedation and Agitation will be measured by the Richmond Agitation Sedation Scale, (RASS) with a score of –2 to –5 reflecting sedation, and +2 to +4 indicative of agitation. Timing of the RASS assignments will align with each CAM assessment for delirium.	As described in the main text, caffeine enhances arousal via key neurochemical pathways. As such, caffeine may mitigate sedation and states related to hypoactive delirium in the early postoperative setting.
Headache	Headache severity will be measured via 10 centimeter visual analogue scale. Assessments will take place 1 hour after PACU arrival and twice daily as aligned with delirium assessments.	Preliminary clinical trial data suggest that caffeine can reduce perioperative rebound headache in habitual caffeine users. ¹⁹
Opioid consumption	Cumulative opioid consumption, in oral morphine equivalents (mg) from PACU arrival through postoperative day three afternoon, will be measured.	Preliminary data suggest that intravenous caffeine, administered during early postoperative recovery, may lead to increased postoperative opioid consumption. ¹⁶
CAM, Confusion Assessment Method; PACU, postanesthesia care unit; RASS, Richmond Agitation Sedation Scale.		

for previous trials.^{2 38–40} 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.⁴¹

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,^{18 19 39} 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),⁴² Montreal Cognitive Assessment⁴³ and Instrumental Activities of Daily Living.⁴⁴ Nausea and vomiting will be assessed via the Postoperative Nausea and Vomiting Intensity Scale⁴⁵ 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 (\pm 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 use⁴⁶). 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 Cochran-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).⁴⁷ Significance level (α) was set at 0.05. A postoperative delirium incidence (including the PACU time frame) of 30% was conservatively estimated based on our preliminary trial.¹⁶ A sample size of 250 participants will provide between 80% and 95% power assuming a control group delirium incidence of 30%, 10–30% 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 $>20\%$.¹⁶ Increased potency may be expected with older patients given the reduced pharmacologic volume of distribution²⁶ and a possible age-caffeine interaction effect with respect to cognition.²⁵ 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.^{17, 48} 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.¹⁷ 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 $n=50$)⁴⁹ based on preoperative AD8 screening, Montreal Cognitive

Box 1 Caffeine, Postoperative Delirium And CHange In Outcomes after Surgery-2 ethical considerations

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

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 complications, such as prolonged hospitalisation, falls and additional cognitive or functional decline.

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 randomised, 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 empanelled to monitor study progress, safety outcomes and adverse events. These additional monitoring strategies will strengthen rigour of trial operations 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 postoperative delirium and related complications⁹; 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 diversity, equity and inclusion efforts.

4. Is there a favourable benefit: risk ratio, such that the risks are acceptably 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 cardiovascular perturbations or other untoward events,^{22 64–66} particularly at moderate doses consistent with those chosen for this trial. A full description 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?

Continued

Box 1 Continued

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 to provide independent review and oversight. The DSMB approved the trial protocol and related documents prior to trial initiation. The DSMB also has the independent authority to recommend amendments and issue a termination recommendation to the National Institute on Aging.

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 reviewed and approved by both the University of Michigan Medical School Institutional Review Board and DSMB. This document also meets requirements outlined in the US Department of Health and Human Services 2018 Common Rule (45 Code of Federal Regulations, 46.116).

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 hospital lifespans. Privacy will be ensured by managing Protected Health Information through secure, confidential procedures outlined in the protocol. 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 registry entry will be provided, such that participants will be able to review study information and results.

Assessment score <23,⁴³ and preserved functional independence via cognitive independent activities in daily living. This subgroup analysis will test the hypothesis that preoperative mild cognitive impairment will be associated with deviations in baseline neural criticality, based on surrogate EEG measures.^{17 50} As a secondary analysis, we will also determine whether caffeine exerts a differential effect on cognitive outcomes in patients with mild cognitive impairment, based on our evidence that caffeine may optimise neural criticality, and criticality breakdowns are postulated to underlie mild cognitive impairment and Alzheimer's disease.^{17 50 51} Delirium incidence, severity and Montreal Cognitive Assessment scores 1-month post-discharge will also be compared in those with and without baseline mild cognitive impairment.

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 participants 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.⁵² 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.

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