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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.

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.

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 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
Hampl *et al* 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 *et al* 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 *et al* 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 *et al* 2018[22]	Caffeine was not associated with a reduced risk of new postoperative atrial fibrillation (n=110 participants).	Postoperative atrial fibrillation	► None
Liu *et al* 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 *et al* 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, postanaesthesia 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

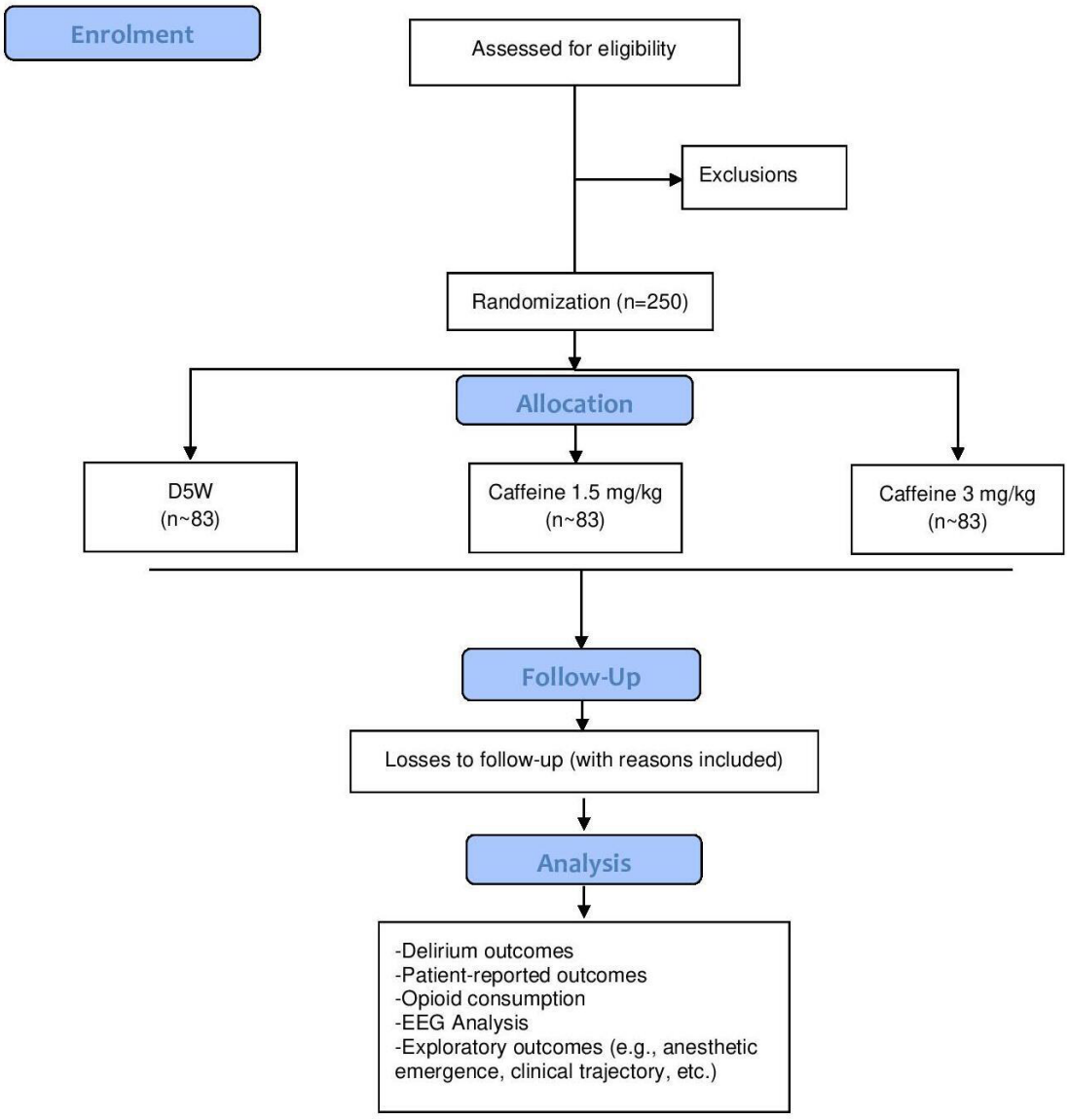

Figure 1 Consolidated Standards of Reporting Trials flow diagram presented. The design is a three-arm parallel design with a 1:1:1 allocation ratio (placebo: low-dose caffeine: high-dose caffeine). D5W, dextrose 5% in water; EEG, electroencephalography.

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 coffee[24]) 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 coffee[24]) 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 (±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).[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

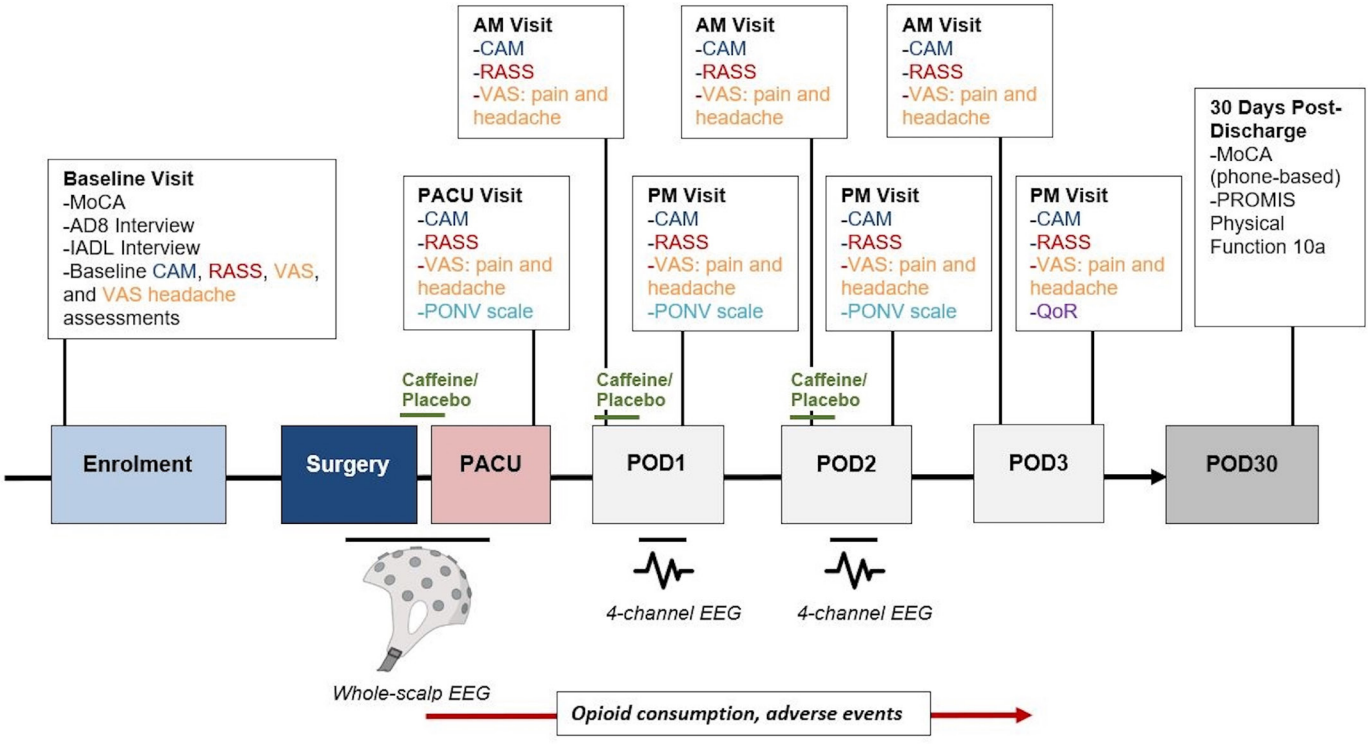

Figure 2 Participant flow through the trial is illustrated. Baseline clinical and cognitive assessments will take place during preoperative enrolment. Whole-scalp, wireless, high-density (72-channel) electroencephalography (EEG) recordings will take place immediately prior to surgery, intraoperatively 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%0[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, postanaesthesia 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 Assessment[43] and Instrumental Activities of Daily Living.[44] Nausea and vomiting will be assessed via the Postoperative Nausea and Vomiting Intensity Scale[45] 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[46]). 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).[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 distribution[26] 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 complications[9]; 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 befits 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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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.

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THE CAFFEINE, POSTOPERATIVE DELIRIUM, AND CHANGE IN OUTCOMES AFTER SURGERY (CAPACHINOS-2) STUDY

Protocol Number: 2.0

National Clinical Trial (NCT) Identified Number: NCT05574400

Principal Investigator: Phillip E. Vlisides, MD

Funded by: National Institute on Aging

Version Number: v.2.0

14 December 2022

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and all terms and conditions of any awards granted. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from any affiliated sponsors, funding agency, and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

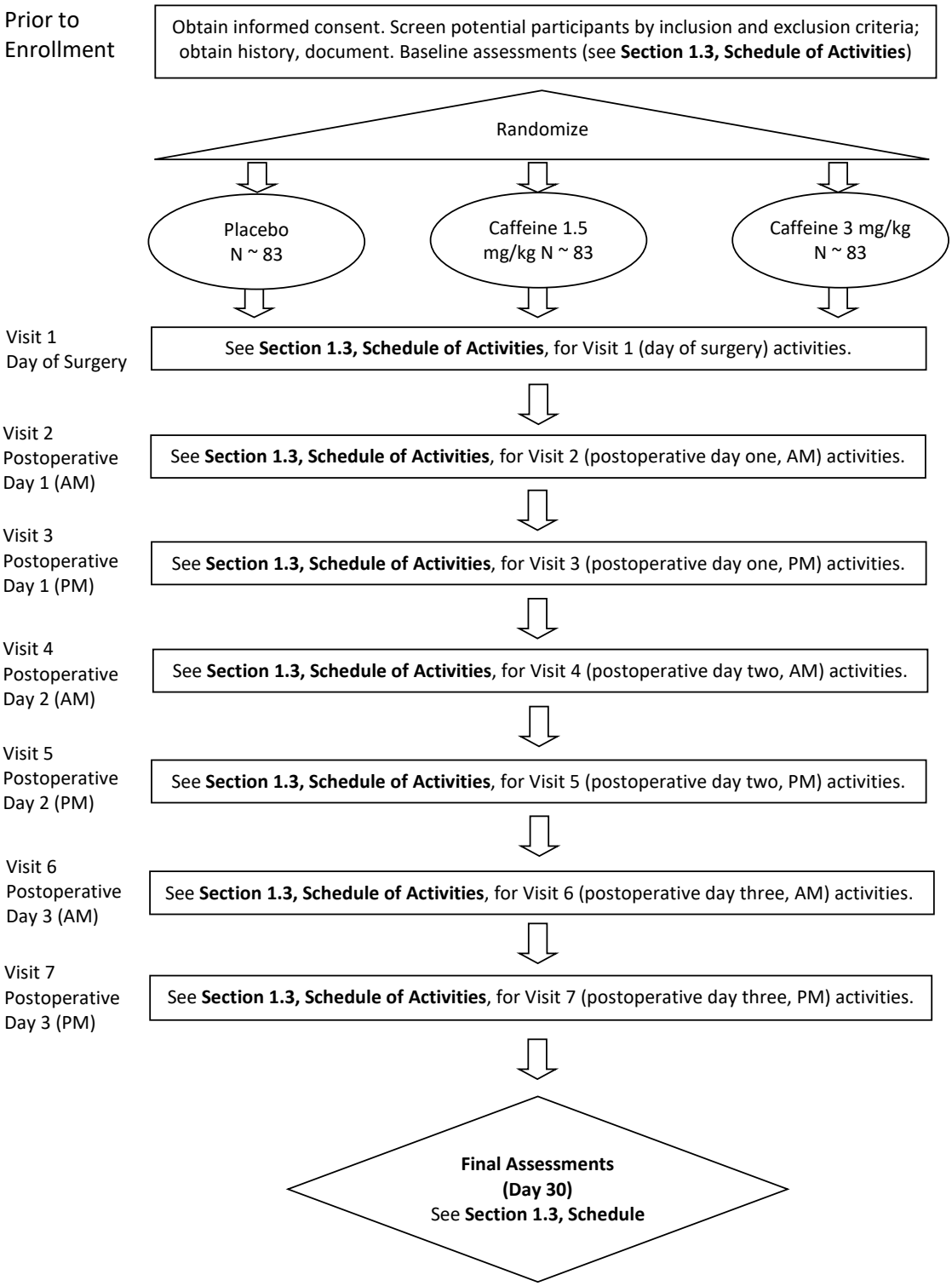
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	The CAffeine, Postoperative delirium, And CHange IN Outcomes after Surgery-2 (CAPACHINOS-2) Study
Study Description:	The objective of this study is to test the effects of caffeine on neurocognitive and clinical recovery after major surgery. Specifically, this trial tests the primary hypothesis that caffeine will reduce the incidence of postoperative delirium.
Objectives:	Primary objective: The primary objective is to determine whether postoperative caffeine reduces the incidence of postoperative delirium, based on standardized delirium assessment methodology. Secondary Objectives: To determine (1) whether caffeine improves postoperative patient satisfaction, based on validated, patient-reported quality of recovery measures, and (2) neural correlates of delirium and Mild Cognitive Impairment, based on advanced electroencephalographic (EEG) analysis.
Endpoints:	Primary Endpoint: Incidence (%) of postoperative delirium, measured via long-form Confusion Assessment Method (CAM).[1] Secondary Endpoints: -- Delirium severity (CAM-S)[2] -- Delirium duration (days, n) -- Patient-reported 15-item Quality of Recovery score[3] -- Agitation (via Richmond Agitation and Sedation Scale, RASS)[4] -- Sedation (via Richmond Agitation and Sedation Scale, RASS)[4] -- Headache severity (10-centimeter visual analog scale, VAS) -- Cumulative opioid consumption (oral morphine equivalents, mg)

Study Population:	In total, surgical patients (n=250; ≥70 years of age) presenting for major non-cardiac, non-intracranial neurologic surgery will be recruited at Michigan Medicine.
Phase:	2
Description of Sites/Facilities Enrolling Participants:	Study operations will be conducted at Michigan Medicine University Hospital and Cardiovascular Center; Ann Arbor, MI USA.
Description of Study Intervention:	This will be a three-arm parallel trial. Participants will be randomized to intravenous dextrose 5% in water (placebo), low-dose caffeine citrate (1.5 mg/kg), or high-dose caffeine citrate (3 mg/kg) at multiple postoperative time points over a 30-minute infusion period.
Study Duration:	The estimated trial duration will be approximately four years.
Participant Duration:	Total study duration for patients will be approximately 30 days.

1.2 SCHEMA


Prior to Enrollment
Obtain informed consent. Screen potential participants by inclusion and exclusion criteria; obtain history, document. Baseline assessments (see **Section 1.3, Schedule of Activities**)
Randomize
Placebo N ~ 83
Caffeine 1.5 mg/kg N ~ 83
Caffeine 3 mg/kg N ~ 83
Visit 1 Day of Surgery
See **Section 1.3, Schedule of Activities**, for Visit 1 (day of surgery) activities.
Visit 2 Postoperative Day 1 (AM)
See **Section 1.3, Schedule of Activities**, for Visit 2 (postoperative day one, AM) activities.
Visit 3 Postoperative Day 1 (PM)
See **Section 1.3, Schedule of Activities**, for Visit 3 (postoperative day one, PM) activities.
Visit 4 Postoperative Day 2 (AM)
See **Section 1.3, Schedule of Activities**, for Visit 4 (postoperative day two, AM) activities.
Visit 5 Postoperative Day 2 (PM)
See **Section 1.3, Schedule of Activities**, for Visit 5 (postoperative day two, PM) activities.
Visit 6 Postoperative Day 3 (AM)
See **Section 1.3, Schedule of Activities**, for Visit 6 (postoperative day three, AM) activities.
Visit 7 Postoperative Day 3 (PM)
See **Section 1.3, Schedule of Activities**, for Visit 7 (postoperative day three, PM) activities.
Final Assessments (Day 30) See **Section 1.3, Schedule**

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Screening/ Enrollment Visit Day -14 to +1	Day of Surgery Visit 1, Day 1	Visit 2 Day 2 POD1 AM	Visit 3 Day 2 POD1 PM	Visit 4 Day 3 POD2 AM	Visit 5 Day 3 POD2 PM	Visit 6 Day 4 POD3 AM	Visit 7 Day 5 POD3 PM	Day 30
Informed consent	X								
Demographics	X								
Medical history	X								
Randomization		X							
Administer study intervention[a]		X	X		X				
Concurrent medication review	X	X	X	X	X	X	X	X	
Physical exam	X	X	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X	X	
Height	X	X							
Weight	X	X							
Cognitive function	X								X
Delirium assessments	X	X	X	X	X	X	X	X	
RASS Score		X	X	X	X	X	X	X	
Quality of Recovery								X	
PONV		X		X		X			
Headache assessments	X	X	X	X	X	X	X	X	
Opioid consumption data	X	X	X	X	X	X	X	X	
Dietary caffeine intake	X	X	X	X	X	X	X	X	
Physical function	X								X
Safety outcomes		X	X	X	X	X	X	X	X
Hospital length of stay and disposition									X
Adverse event review and evaluation	X	X	X	X	X	X	X	X	X
Complete Case Report Forms (CRFs)	X	X	X	X	X	X	X	X	X

On the day of surgery, assessments will occur one hour after postanesthesia care unit admission. Postoperative day (POD) assessments will occur between 7:00 – 10:00 AM, and afternoon assessments will occur between 3:00 – 6:00 PM. Outcomes will be ascertained either via in-person data collection or chart review as outlined in **Section 8.1, Efficacy Assessments.** [a]A research nurse or physician assistant will oversee the drug administration and monitor blood pressure (every 5 minutes), heart rate, heart rhythm (via 5-lead electrocardiography), and continuous pulse oximetry. [b]See **Sections 8.2 and 9.4.4** for safety outcomes and assessments. Of note, primary and secondary outcomes are primarily reported in this table. Lastly, the 30-day visit can be conducted virtually and/or by telephone as well.

2 INTRODUCTION

2.1 STUDY RATIONALE

Delirium is a syndrome characterized by failure of basic cognitive functions that affects approximately 20-50% of older surgical patients.[5,6] Delirium during surgical recovery is associated with increased mortality,[7] cognitive and functional decline,[8,9] and prolonged hospitalization.[10] In fact, 3-year survival rates for acutely hospitalized patients with delirium, and subsyndromal delirium, are both less than 50%.[11] Delirium also creates a substantial economic burden, with total healthcare cost estimates ranging from $38 – $152 billion annually.[12] Older age is predictive of delirium after surgery,[13-15] 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 reducing risk of early postoperative delirium. Caffeine promotes arousal via adenosine receptor antagonism[16] and improves cognitive function concurrent with increased cortical cholinergic tone.[17-19] Our preliminary data suggest that caffeine reduces risk of postanesthesia care unit (PACU) delirium in adult non-cardiac surgery patients by optimizing cortical dynamics for cognition.[20,21] Caffeine also optimizes key neurocognitive processes that support information processing[22-24] and may improve other, related aspects of clinical recovery, such as rebound headache in habitual caffeine users.[25] The objective of this trial is to thus test the effects of caffeine on neurocognitive and clinical recovery after major surgery. Specifically, the primary hypothesis is 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 correlates of delirium and Mild Cognitive Impairment via advanced electroencephalographic (EEG) analysis).

2.2 BACKGROUND

Basic science data demonstrate that caffeine promotes wakefulness via adenosine A_{2A} receptor antagonism,[16] and caffeine also improves arousal and cognitive function via increased cortical cholinergic tone (Fig. 1).[17-19] Caffeine also confers acute anti-nociceptive properties and mitigates risk of postoperative mechanical pain hypersensitivity in a rat model.[26] This is highly relevant to the early postoperative setting, as pain is a common postoperative complication that can impair cognitive function in older adults.[27,28]

In a rat model, Wang et al. demonstrated that caffeine accelerated recovery from both propofol and isoflurane anesthesia in a dose-dependent manner.[29] This acceleration, across two different anesthetic classes, occurred without significant changes in hemodynamic physiology. This work was recently translated to healthy volunteers, where caffeine was also found to accelerate emergence time from isoflurane anesthesia (>40% reduction).[30] Participants emerged from anesthesia at higher expired isoflurane concentrations and were able to participate in

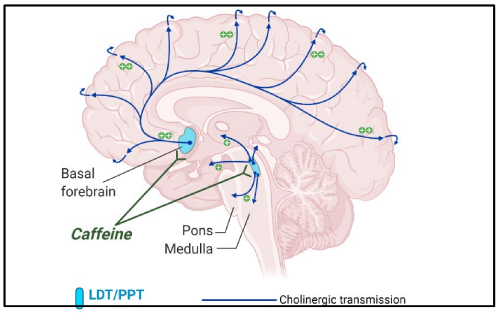


Fig. 1. Caffeine increases cholinergic output from the basal forebrain and lateraldorsal tegmentum and pedunculopontine tegmentum *via* adenosine receptor antagonism. Increased cortical cholinergic tone leads to arousal and improved cognitive function.

psychomotor testing earlier upon receiving caffeine. Encouragingly, no statistically significant differences in cardiac or pulmonary physiologic recovery patterns were appreciated.

A recent single-center clinical trial was designed to test the effects of caffeine on early neurocognitive recovery after major laparoscopic surgery in adults.[20] Results demonstrated that caffeine significantly reduced the risk of PACU delirium (Fig. 2). However, PACU delirium was a post-hoc, exploratory outcome, with a low fragility index[31] between placebo and caffeine groups. Nonetheless, patients randomized to caffeine also demonstrated increased neurophysiologic signs of arousal based on EEG analysis in the PACU.[20] A secondary analysis of the EEG data demonstrated increased neurophysiologic *criticality*, which reflects a point of dynamic instability that may allow for flexible access to a wide range of brain states (and thus, improved cognitive function).[21] Lastly, in this trial, caffeine was not found to reduce opioid consumption, subjective pain reporting, or anesthetic emergence time. However, the small sample size (n=65) precludes firm conclusions. Of note, no major adverse events were reported in relation to caffeine, and early postoperative hemodynamic recovery patterns were similar compared to placebo.

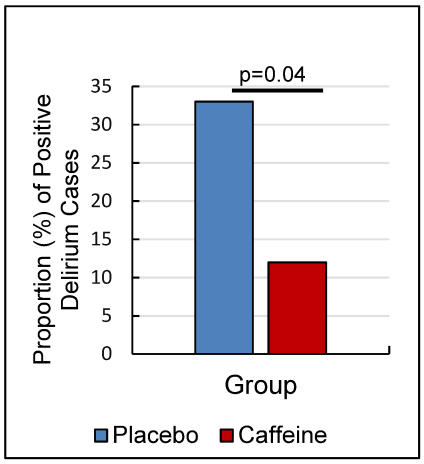


Fig. 2. PACU delirium was significantly reduced in patients receiving intravenous caffeine (4/33, 12%) compared to placebo (10/30, 33%; p=0.04) during surgical closure.

Three previous single-center clinical trials were also designed to test the effects of caffeine on postoperative recovery profiles. A trial by Weber et al. demonstrated a reduced risk of postoperative headache in ambulatory surgery patients at risk for withdrawal headaches (based on baseline intake) after receiving caffeine compared to placebo (10% vs. 23%, p<0.05).[25] No difference was noted in terms of PACU recovery time. Steinbrook et al. studied the effects of caffeine on postoperative nausea and vomiting, finding that caffeine was associated with an increased risk of nausea (26% vs. 10%, p=0.02), but no statistically significant difference was found for the incidence of vomiting, rescue antiemetic use, headaches, fatigue, time to discharge or satisfaction scores (0-10 ordinal scale).[32] Between these two trials, multiple (and relevant) outcomes were not studied, such as anesthetic emergence time, perioperative neurocognitive function, opioid consumption, comprehensive pain measures, or overall patient-reported quality of recovery using rich, multidimensional scales with validation and minimal clinically important difference data.[33-35] Furthermore, these trials were restricted to outpatient surgery, so the aforementioned outcomes were not studied for inpatient surgery. Lagier and colleagues performed a single-center randomized trial to determine whether caffeine reduces postoperative atrial fibrillation in cardiac surgery patients.[36] Caffeine was administered every eight hours (400 mg tablets orally or via nasogastric tube) for a total of six doses. Caffeine did not reduce atrial fibrillation incidence, but, importantly, major adverse events (e.g., arrhythmias, renal injury, hypoxemia) were similar to the placebo group. Postoperative nausea and vomiting risk was higher in the caffeine group compared to placebo (27% vs. 7%, respectively, p=0.005).

Overall, there are converging clinical-translational data to suggest that caffeine may enhance postoperative neurocognitive recovery. However, previous clinical trials have not focused on delirium as the primary outcome, nor have they incorporated tools such as EEG to determine how caffeine might affect underlying cortical dynamics during surgical recovery. The proposed trial will address these gaps; delirium will be the prespecified primary outcome, measured by a validated assessment tool (see

Section 8.1, Efficacy Assessments), and a high-density, whole-scalp EEG system will be used to elucidate cortical dynamics during early postoperative recovery.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Contraindications, drug interactions, and adverse reactions are described in the caffeine citrate package insert (https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=38b39044-737a-4247-a6c4-c86f5e92490e&audience=consumer). Primary risks described relate to the pediatric (neonatal) population, which will not be included in this trial.

In the acute setting, caffeine has been associated with various side effects. As mentioned previously, Steinbrook et al. demonstrated that perioperative caffeine may increase the risk of nausea, though participants randomized to caffeine experienced neither an increased risk of vomiting nor increased rescue antiemetic use.[32] Lagier et al. also demonstrated that postoperative caffeine may increase nausea and vomiting risk; however, the dose and frequency used (400 mg every eight hours, six total doses) are higher than the current trial.[36] Additional safety data have been published in various adult settings. McLellen et al. provide a thorough review of the adult literature relating to caffeine use and side effects.[37] The following side effects and risks of acute caffeine intake have been documented:

- Anxiety
- Irritability
- Gastrointestinal distress
- Tremors
- Nervousness
- Sleep disruption

Side effects have generally occurred with relatively high doses (600 mg)[38,39] and/or in participants with excessive sensitivity (e.g., genetic polymorphisms, non-regular consumers).[40,41] Case reports have demonstrated associations between caffeine intake and increased seizure frequency, particularly in the setting of (1) relatively high doses and (2) pre-existing history of epilepsy.[42,43] A subsequent large population-based study did not reveal an adjusted association with habitual caffeine intake and seizure history.[44] Whether caffeine acts as a common seizure trigger is unclear,[45] but additional precipitating factors (e.g., sleep disturbances) are common in the perioperative setting[46] which may exacerbate epileptiform activity and seizure risk.

The effects of acute caffeine intake on cardiac arrhythmia risk have also been studied for several years across diverse patient populations. The table below summarizes studies examining acute caffeine administration in relation to cardiovascular physiologic perturbations.

Year	Authors	Sample size (n)	Description
1983	Dobmeyer DJ et al.	19	Caffeine (200 mg) modulated atrial refractory periods, but conduction intervals remained unchanged. Two participants receiving caffeine experienced non-sustained ventricular tachycardia after programmed ventricular stimulation, and six participants experienced sustained supraventricular

			tachycardia after caffeine and programmed stimulation.
1987	Myers MG et al.	70	No association with caffeine (300 mg) and ventricular ectopic activity in patients with a recent myocardial infarction. Increases in plasma catecholamines, systolic blood pressure (116 ±2 vs. 123 ±2 mmHg), and diastolic blood pressure (70 ±1 mmHg vs. 74 ±1 mmHg); no changes in heart rate observed.
1989	Graboys TB et al.[47]	50	No association with caffeine (200 mg) and ventricular arrhythmia risk during exercise in patients with malignant ventricular arrhythmia history. Increased catecholamine levels appreciated up to 3 hours after caffeine administration.
1990	Myers MG and Harris L[48]	35	No association with caffeine (450 mg) and ventricular arrhythmias in patients with recent myocardial infarction.
1990	Chelsky LB et al.[49]	22	In patients with ventricular arrhythmia history, caffeine (275 mg) did not significantly alter the inducibility or severity of ventricular arrhythmias.
2018	Lagier et al.[36]	55 (caffeine arm)	Randomized clinical trial to determine whether perioperative caffeine would reduce the incidence of postoperative atrial fibrillation. Caffeine (400 mg) was administered orally or via nasogastric tube, beginning intraoperatively and every eight hours thereafter for six total doses. Major adverse events (e.g., atrioventricular block, hypoxemia, renal injury) were similar between placebo and caffeine groups.
2002	Corti R et al.[50]	15	Both coffee and caffeine (275 mg) increased sympathetic nerve activity and systolic blood pressure (6.4 ±1.7 mm Hg) one hour after administration. Heart rate decreased (-4.6 ± 2 bpm) one hour after administration.
2015	Lemery R et al.[51]	80	No association with oral caffeine (5 mg/kg) and supraventricular tachycardia risk in patients with prior history. Furthermore, caffeine did not modulate refractory periods or nodal conduction. Caffeine was associated with increase systolic (143 [128-165] mmHg vs. 132 [114-150] mmHg) and diastolic (83 [77-94] mmHg vs. 74 [69-86] mmHg) blood pressure. Heart rate remained unchanged.

2016	Dixit S et al.[52]	1388	No association between habitual caffeine consumption and premature ectopic beats during a 24-hour holter monitoring period.
2016	Zuchinali P et al.[53]	51	In patients with moderate-to-severe left ventricular systolic dysfunction, caffeine (500 mg) was not associated with risk of new arrhythmias.

Importantly, these data suggest that acute caffeine intake is not associated with adverse cardiovascular events, even in the setting of pre-existing cardiac pathology (e.g., recent myocardial infarction, ventricular arrhythmia history, recent coronary artery bypass surgery). Acute caffeine administration may lead to increased serum catecholamine levels and modest increases in blood pressure.

In the perioperative setting, caffeine has been studied in relation to perioperative headache, nausea and vomiting risk, gastrointestinal function, and, in the cardiac population, risk of new-onset atrial fibrillation.

Year	Authors	Sample size (n)	Description
1993	Weber et al.[54]	105 (caffeine arm)	Observational study to determine whether habitual (oral) caffeine intake, on the day of surgery, would reduce the incidence and severity of perioperative headache. Caffeine intake was associated with reduced headache incidence. Adverse events were not reported in the study.
1995	Hampl et al.[55]	20 (caffeine arm)	Randomized clinical trial, whereby habitual caffeine users were randomized to caffeine tablets (dose matched to daily intake) or placebo on the day of surgery and on the first postoperative morning. Perioperative headache was significantly reduced in patients randomized to caffeine. Adverse events were not reported.
1997	Weber et al.[25]	114 (caffeine arm)	The trial objective was to determine whether caffeine would mitigate risk of postoperative headache and reduce recovery time. Patients were randomized to intravenous caffeine (200 mg) or placebo administered in the PACU upon admission. Habitual users were less likely to experience a postoperative headache if randomized to caffeine. Adverse events were not reported in the trial.
2013	Steinbrook et al.[32]	62 (caffeine arm)	The trial objective was to determine whether intravenous caffeine sodium benzoate (500 mg), given 15 minutes prior to anesthetic emergence, would reduce risk of postoperative nausea or vomiting during outpatient surgery. Nausea was more common in the caffeine group, and

			caffeine did not improve headache, fatigue, satisfaction, or time to discharge. Adverse events were not reported in the trial.
2018	Lagier et al.[36]	55 (caffeine arm)	Randomized clinical trial to determine whether perioperative caffeine would reduce the incidence of postoperative atrial fibrillation. Caffeine (400 mg) was administered orally or via nasogastric tube, beginning intraoperatively and every eight hours thereafter for six total doses. Major adverse events (e.g., atrioventricular block, hypoxemia, renal injury) were similar between placebo and caffeine groups.
2021	Liu et al.[56]	40 (caffeine arm)	Adult gastrointestinal surgery patients demonstrated improved recovery time of gastrointestinal function with randomization to daily green tea postoperatively. No adverse events reported.
2021	Vlisides et al.[20]	33 (caffeine arm)	Non-cardiac surgery patients receiving intravenous caffeine (200 mg) during surgical closure demonstrated reduced PACU delirium. No major adverse events in relation to caffeine. Furthermore, postoperative hemodynamic recovery profiles were similar compared to placebo patients.

In summary, perioperative caffeine administration is associated with reduced headache in habitual caffeine users. Caffeine may also increase the risk of postoperative nausea and/or vomiting. Both intravenous and oral administration routes have been utilized. Adverse events were not reported in many of these studies, though no major adverse events were reported based on available data.

In the chronic setting, caffeine has also been studied in relation to cardiovascular health and outcomes. Major, representative studies are outlined below:

Year	**Authors**	**Sample size (n)**	**Description**
1999	de Vreede-Swagemakers JJ et al.[57]	117	>10 cups of coffee per day was associated with sudden cardiac arrest in patients with coronary artery disease
2005	Frost L and Vestergaard P[58]	47,949	No association between caffeine consumption and risk of atrial fibrillation or flutter
2006	Lopez-Garcia E et al.[59]	128,493	No association between coffee consumption and coronary heart disease
2010	Reis JP et al.[60]	5,115	No substantial association between coffee or caffeine intake and coronary and carotid atherosclerosis

2011	Klatsky AL et al.[61]	130,054	An inverse relationship was demonstrated between habitual caffeine intake and hospitalization for arrhythmias

Chronic caffeine consumption does not appear to be associated with adverse cardiovascular outcomes in the non-surgical setting.

Overall, the weight of available evidence suggests that caffeine administration is not associated with major adverse cardiovascular perturbations (in both acute and chronic settings), particularly at moderate doses consistent with those chosen for this trial. In the perioperative setting, caffeine may reduce risk of rebound headache in habitual users, though caffeine has also been associated with increased postoperative nausea and vomiting. Additional side effects, such as tremors, nervousness, gastrointestinal distress, anxiety, irritability, and sleep disruption remain possible.

2.3.2 KNOWN POTENTIAL BENEFITS

Participants may experience a number of benefits specific to the perioperative setting. Categories of benefits, with supporting data, are described below:

Cognitive Function

Across various doses and settings, caffeine has been demonstrated to improve arousal, reaction time, vigilance, attention, hedonic tone (e.g., mood), and physical recovery (e.g., ergogenic effects).[37] These properties may be particularly useful in the early perioperative setting, where cognitive impairment is common. In fact, data from our preliminary trial suggest that caffeine reduces the incidence of delirium in the PACU concurrent with electroencephalographic evidence of increased neurocognitive arousal.[20]

Anesthetic Emergence

Caffeine (7.5 mg/kg) has recently been shown to accelerate anesthetic emergence time (~40%) in healthy human volunteers.[30] After caffeine administration, participants were also able to participate in psychomotor testing earlier compared to placebo. These findings are supported by basic science data that demonstrate a dose-response relationship in relation to anesthetic emergence acceleration.[29,62]

Analgesia

Basic science data demonstrate that caffeine confers acute anti-nociceptive properties and protection against hypersensitivity in the days following surgery in both sleep-deprived and non-sleep-deprived rat models.[26] Recent Cochrane Reviews have also found that caffeine provided significant analgesic benefit as part of a multimodal strategy in both surgical[63] and non-surgical settings.[64] For obstetric and oral surgery patients, the number needed to treat for achieving at least 50% pain relief (4-6 hours) was 2.2 (1.8 to 2.5), with a relative effect (risk ratio) of 5.5 (3.5 to 8.7).[63] Participants receiving caffeine were also less likely to require analgesic re-medication within eight hours (number needed to prevent, 2.9 [2.2 to 4.3]).[63] However, data from a single-center randomized trial demonstrate that an intravenous infusion of caffeine, administered prior to anesthetic emergence, did not significantly reduce postoperative pain scores or opioid consumption.[20] Lastly, caffeine may also ameliorate rebound perioperative headache, particularly for patients who habitually consume caffeine.[25]

Thus, there is preliminary evidence – and associated biologic plausibility – to suggest that caffeine may improve postoperative neurocognitive recovery and quality of recovery (e.g., reduced rebound headache).

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Given the potential benefits of caffeine outlined above, along with the high safety profile described, perioperative caffeine suggests a favorable benefit-to-risk ratio, particularly while observing appropriate eligibility criteria and clinical oversight as proposed in this trial. The study- and site-PIs will review eligibility criteria to ensure appropriate medical screening and trial enrollment.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To determine whether intravenous caffeine reduces the incidence of postoperative delirium	--The primary endpoint is delirium, as measured via long-form Confusion Assessment Method (CAM), obtained one hour after PACU admission and twice daily for the first three postoperative days. The CAM will be complemented by a validated chart review method[65,66] 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%.[1,67,68]
Secondary		
To determine whether caffeine reduces delirium severity	-- A secondary endpoint will be delirium severity, as measured via the same long-form CAM (CAM-S score).	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.[2]
To determine whether caffeine reduces delirium duration	-- An additional secondary endpoint related to delirium will be delirium duration, as measured by the cumulative number of days (n) with a positive delirium screen.	Delirium duration is associated with poor hospital outcomes.[69]

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
To determine whether intraoperative caffeine improves patient-reported quality of recovery	-- Patient-reported 15-item Quality of Recovery score,[3] which will be assessed in the afternoon on postoperative day two.	The original Quality of Recovery[33] scale has been used for 20 years in perioperative clinical trials research. Extensive validity,[70] reliability,[70] and minimal clinically important difference data[35] have been published. This scale was also recently endorsed by the Standardized Endpoints in Perioperative Medicine Initiative.[71] Caffeine is postulated to ameliorate pain and postoperative confusion, which are each independently associated with poor recovery on this scale.[34]
To determine whether caffeine impacts sedation or agitation postoperatively	-- Sedation (-2 to -5), Richmond Agitation and Sedation Scale (RASS). Assessed one-hour after PACU arrival and twice daily. Timing will be aligned with CAM delirium assessment. -- Agitation (+2 to +4), RASS. Assessed one-hour after PACU arrival and twice daily. Timing will be aligned with CAM delirium assessment.	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.
To determine whether caffeine reduces risk of perioperative headache	-- Headache severity (n, 10-centimeter VAS) one-hour after PACU arrival and twice daily. Timing will be aligned with CAM delirium assessment.	Preliminary clinical trial data suggest that caffeine can reduce perioperative rebound headache in habitual caffeine users.[25]
To determine the effects of caffeine on postoperative opioid consumption.	-- Cumulative opioid consumption, oral morphine equivalents (mg) from PACU arrival through postoperative day two afternoon.	Preliminary data suggest that intravenous caffeine, administered during

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
		early postoperative recovery, may lead to increased postoperative opioid consumption.[20]
Tertiary/Exploratory		
To determine the impact of intravenous caffeine on anesthetic emergence profiles	-- Anesthetic emergence time (minutes; time from surgical closure finish to extubation) -- Time from PACU arrival until PACU discharge criteria met (minutes)	Will help to characterize early postoperative arousal and clinical trajectory
To determine whether caffeine reduces the risk of immediate postoperative pulmonary complications	-- Composite outcome: any occurrence of the following airway/pulmonary complications from extubation through PACU stay: airway adjunct use, unplanned continuous positive airway pressure device, unplanned humidified high-flow oxygen, need for bag-mask ventilation, or reintubation.	Given the arousal effects of caffeine previously discussed, caffeine may plausibly mitigate risk of adverse airway and pulmonary complications in the immediate postoperative setting.
To determine whether caffeine impacts overall hospital length of stay	--Hospital length of stay (days)	Delirium is associated with prolonged hospitalization. If caffeine successfully reduces delirium burden, hospital length of stay may theoretically be reduced.
To determine whether caffeine impacts post-discharge clinical trajectory	--30-day cognitive function (score, n) based on the Montreal Cognitive Assessment --30-day physical function (score, n) based on the PROMIS Physical Function 10a	If caffeine improves outcomes (e.g., delirium, length of stay) during hospitalization, discharge trajectory may also be improved.
To determine whether caffeine impacts discharge disposition	Discharge disposition (e.g., home, skilled care facility)	If caffeine improves outcomes (e.g., delirium, length of stay) during hospitalization, discharge disposition may also be optimized

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4 STUDY DESIGN

4.1 OVERALL DESIGN

The **central hypothesis** of this study is that intravenous caffeine will reduce the incidence of postoperative delirium. This will be a Phase II, single-center, quadruple-blinded, placebo-controlled, block-randomized trial. Written informed consent will be obtained from all participants, and institutional review board approval will be obtained. The trial will follow a parallel design, and participants will be block-randomized with a 1:1:1 allocation ratio (placebo: 1.5 mg/kg caffeine: 3 mg/kg caffeine).

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This trial will follow conventional (rather than adaptive) methodologies, for the following reason: even if caffeine is not found to reduce risk of postoperative delirium, secondary outcomes (e.g., quality of recovery, headache) may nonetheless suggest benefit and warrant further analysis. Lastly, multiple dosing arms will help to elicit optimal dosing strategies for maximizing the benefit-to-risk ratio across outcomes.

The control group will not receive either caffeine intervention and will remain at standard risk for perioperative complications previously outlined. However, control group patients will nonetheless receive standard perioperative care that would otherwise be received without trial enrollment. Dextrose 5% in water (D5W) was chosen as the placebo intervention, as caffeine citrate is soluble in D5W solution.

4.3 JUSTIFICATION FOR DOSE

The study drug, either caffeine citrate or D5W (placebo), will be administered as an intravenous infusion starting at the beginning of surgical closure and again on the first two postoperative mornings. The infusion will be given over a 30-minute timespan. The two caffeine arms, 1.5 mg/kg and 3 mg/kg were carefully chosen based on preliminary data and literature review. Dosing will be based on total body weight.[72]

The lower dose of 1.5 mg/kg may be appropriate for such an older population. First, the reduced dose might lower the risk of adverse side effects (e.g., nausea, vomiting, anxiety).[36] Second, our preliminary trial was based on a younger population (mean [±standard deviation] age [years]: 52 ±17), and the cognitive effects of caffeine may be more pronounced in older populations.[73] Lastly, serum caffeine concentration increases with age, as the total volume of caffeine distribution is reduced in older patients.[74] As such, higher peak serum caffeine concentrations are observed with advancing age after both intravenous and oral administration.[74]

The higher dose of 3 mg/kg might provide added cognitive benefit.[37] In fact, the mean, weight-based dose for participants receiving caffeine *and not experiencing any delirium* in our preliminary trial was 3 mg/kg.[20] Additive cognitive benefit has also been observed with this dose, particularly for domains relevant to delirium (e.g., attention, vigilance)[75-78] and after sleep deprivation,[79] which is commonly experienced in the hospital setting. Nonetheless, this higher dose may also be associated with additional side effects (e.g., anxiety, GI distress, nausea/vomiting), so multiple dosing arms will help to determine optimal perioperative doses that maximize benefit-to-risk ratios across each postoperative day.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3.

The end of the study is defined as completion of the last visit or procedure shown in the SoA.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Male or female, ≥70 years of age
4. Presenting for non-cardiac surgery, non-intracranial neurologic, non-major vascular (e.g., operations below the diaphragm) surgery with planned admission for at least 72 hours.

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Emergency surgery
2. Outpatient surgery
3. Severe cognitive impairment precluding the capacity for informed consent
4. Seizure disorder history
5. Intolerance or allergy to caffeine (based on subjective reporting or objective documentation)
6. Weight >130 kg (as a 3 mg/kg dose would approach the upper limit of daily intake recommended by the FDA)
7. Enrollment in conflicting research study
8. Patients in acute liver failure
9. Acute kidney injury preoperatively
10. Diagnosis of pheochromocytoma
11. Severe audiovisual impairment
12. Non-English speaking

5.3 LIFESTYLE CONSIDERATIONS

Enrolled participants may be patients who do not consume caffeine or those who are habitual caffeine users. A dedicated analysis plan will be used to test associations between habitual caffeine use and specific outcomes of interest (see **Section 9.4, Statistical Analyses**).

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. Screen failure information will be provided to (1) ensure transparent reporting, (2) meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and (3) respond to queries from regulatory

authorities. Reportable information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Our research group has established a robust infrastructure for recruiting surgical patients for perioperative clinical trials.[6,80] For example, our department recruited >20,000 surgical patients for the Michigan Awareness Control Study over a two-year period.[80] Our department then served as one of two leading sites in a multicenter trial for preventing postoperative delirium, and >100 patients were recruited in a two-year period (with many of the same outcomes and assessment tools proposed in this study).[6] Our research team has also recruited hundreds of patients for various smaller-scale trials and observational studies over the past few years.[20,81-86] This local infrastructure for clinical trial recruitment and enrollment is firmly established, as we coordinate with preoperative clinics at Michigan Medicine to maintain weekly recruitment. Thus, we do not anticipate issues with recruitment or retention.

Additionally, targeted efforts will be made to enhance participant diversity and include historically under-represented patient populations. Such recruitment will be facilitated through the University of Michigan Office of Health Equity and Inclusion. This department aims to increase representation of historically underrepresented and underserved communities. Additionally, the Michigan Institute for Clinical and Health Research has established relationships with local communities that include underrepresented populations in research. By working with these programs, our goal is to bolster participant diversity via targeted connection with the community.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

Participants will be block randomized with a 1:1:1 allocation ratio (placebo: low-dose caffeine: high-dose caffeine) in a three-arm parallel design. Prepared intravenous syringe solutions of 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 given with scheduled, morning medications as administered and overseen by the research nurse (or physician assistant).

6.1.2 DOSING AND ADMINISTRATION

The study drug will be administered as an intravenous infusion, using an infusion pump, over 30 (±5) minutes beginning during surgical closure and on the first two postoperative mornings. Low-dose caffeine will consist of 1.5 mg/kg caffeine base, and high-dose caffeine will contain 3 mg/kg caffeine base; both caffeine drugs will be dissolved in 40 mLs of dextrose 5% in water. No dose or timing changes are anticipated, and the infusion will be administered over the entire 30 (±5) minutes. A research nurse or physician assistant will oversee the drug administration and monitor blood pressure (every 5 minutes), heart rate, heart rhythm (via 5-lead electrocardiography), and continuous pulse oximetry.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

Caffeine citrate injection (Fresenius Kabi) or generic equivalent (if the Fresenius Kabi product is not available) will be purchased by the Research Pharmacy using the study funds. Study drugs will be prepared, stored, and dispensed per hospital research pharmacy guidelines and protocols (see 6.2.3 and

6.2.4). Unused drugs will be sent back to the research pharmacy and discarded per pharmacy protocols and standards.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Per manufacturer (Fresenius Kabi USA, LLC) package insert: Caffeine citrate injection is indicated for the treatment of apnea of prematurity (https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=38b39044-737a-4247-a6c4-c86f5e92490e&audience=consumer). Caffeine citrate injection, USP for intravenous administration is a clear, colorless, sterile, nonpyrogenic, preservative-free, aqueous solution adjusted to pH 4.7. Each mL contains 20 mg caffeine citrate (equivalent to 10 mg of caffeine base) prepared in solution by the addition of 10 mg caffeine anhydrous to 5 mg citric acid monohydrate, 8.3 mg sodium citrate dihydrate and Water for Injection, USP. Caffeine, a central nervous system stimulant, is an odorless white crystalline powder or granule, with a bitter taste. It is sparingly soluble in water and ethanol at room temperature. The chemical name of caffeine is 3,7-dihydro-1,3,7-trimethyl-1H-purine-2,6-dione. In the presence of citric acid it forms caffeine citrate salt in solution. Vials should and will be inspected visually for particulate matter prior to use.

6.2.3 PRODUCT STORAGE AND STABILITY

Caffeine citrate injection, USP, is stored according to manufacturer recommendations in 3 mL single-dose vials. The drug will be stored in the hospital research pharmacy in accordance with hospital pharmacy practice and guidelines. Caffeine citrate is stable at room temperature over a 24-hour period.[87]

6.2.4 PREPARATION

The assigned caffeine citrate dose will be diluted in dextrose 5% in water to a total volume of 40 mL. These procedures will occur via standard Michigan Medicine Research Pharmacy protocols, procedures, and operations.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

As previously described, participants will be block-randomized with a 1:1:1 allocation ratio (placebo: caffeine 1.5 mg/kg: caffeine 3 mg/kg). Randomization will also be stratified by age (<75 or ≥75 years old) and sex. Older age is a risk factor for delirium, with patients 75 years of age and older having particularly high risk.[13-15] Response to caffeine may also differ based on sex.[88] Stratified randomization will thus help to balance these biologically relevant, prognostic variables and mitigate selection bias. Additionally, research teams, patients, clinicians, and analysts will remain blinded to the study drug intervention. Regression models will also include adjustments for relevant confounders, and baseline imbalances, as described in **Section 9, Statistical Considerations.** Blinding can be broken, if necessary, per the physicians caring for the subject to ensure subject safety.

6.4 STUDY INTERVENTION COMPLIANCE

The research teams will use a mandatory case report form (CRF) to indicate that the study drug was given. Furthermore, the beginning and end times of the study drug infusion will be recorded for each participant. Reasons for deviation (e.g., not administering the study drug, incorrect administration timing) will also be reported and reported.

6.5 CONCOMITANT THERAPY

No other study drugs will be given. Participants will receive medications as clinically indicated by perioperative providers. Caffeine is metabolized via Cytochrome P450 1A2, and medications that inhibit, induce, or serve as substrates for this system may affect caffeine metabolism (*https://drug-interactions.medicine.iu.edu/MainTable.aspx*). Co-administration of these medications will be recorded and considered during data analysis.

6.5.1 RESCUE MEDICINE

Not applicable

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Discontinuation of the study drug may occur for the following reasons:

- Participant is found to not meet all eligibility criteria
- Adverse cardiac event (e.g., unstable arrhythmia)
- Adverse neurologic event (e.g., seizure)
- Additional adverse events (e.g., hypersensitivity, allergic reaction)
- Clinician caring for the patient has requested discontinuing the drug due to safety concerns
- Discontinuation at the discretion of the study- or site-PI for additional concerns

Discontinuation from caffeine administration does not necessarily mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified after enrollment (i.e., adverse reaction to the study drug), the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE). The study drug may be restarted if deemed safe and appropriate by both the (1) clinical team caring for the patient and the (2) site-PI of the respective study site.

The data to be collected at the time of study intervention discontinuation will include the following:

- Time of drug initiation and discontinuation
- Reason for discontinuation
- Person (e.g., clinician, investigator) who requested that the drug be stopped

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request. Additionally, an investigator may discontinue or withdraw a participant from the study for the following reasons:

- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for participant discontinuation or withdrawal from the study will be recorded on the designated case report form (CRF). Participants who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. For participants who sign the informed consent form, are randomized, receive the study intervention, and subsequently withdraw (or are withdrawn or discontinued from the study), these participants will not be replaced if they have completed the primary outcome assessment. If such a participant is withdrawn or discontinued prior to assessing the primary outcome, that participant will be replaced.

7.3 LOST TO FOLLOW-UP

There is a close proximity in time between study intervention (i.e., study drug infusion) and early postoperative assessments. This assessment will occur when the patient is still hospitalized early in the postoperative course. Thus, loss to follow-up is not anticipated to be a major concern for the primary outcome in this study. However, such loss may occur in certain scenarios, such as unplanned intensive care unit admission with patients remaining intubated postoperatively. Loss to follow-up will thus be reported in study flow diagrams and is accounted for in power calculations (see **Section 9, Statistical Considerations**).

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

The specific timing of procedures/evaluations to be done at each study visit are outlined in **Section 1.3, Schedule of Activities (SoA).** Details regarding major trial assessment measures are described in the following section.

Screening/Enrollment Visit

Screening visits will be performed during either preoperative clinic visits or on the morning of surgery. Trained research team members will make a determination of study eligibility based on medical chart review and concurrent discussion with potential participants. Screening forms will then be reviewed, confirmed, and signed by the study PI (Vlisides) anytime between the initial screening visit and surgical intervention. During this initial visit, baseline vitals will be taken and a physical exam will be performed by clinic and perioperative clinicians per clinical standards. Baseline research case report forms will be completed, as outlined in **Section 1.3, Schedule of Activities (SoA)**, by trained research team members.

Delirium Assessments

Delirium will be assessed using the long-form CAM, via in-person assessment, during hospitalization. The CAM strategy will be used to assess delirium severity,[2] and total delirium duration (days) will also be calculated.

Quality of Recovery

The patient-reported 15-item Quality of Recovery scale will be used.[3] This scale has been chosen as a key secondary outcome assessment, as caffeine is postulated to reduce delirium and, potentially, headache, which may help with the recovery process. The scale will be administered preoperatively at baseline and on the second postoperative afternoon. Results will be ascertained and recorded via in-person assessment by the research team.

Agitation and Sedation

Given that caffeine enhances arousal, as described previously, caffeine may also prevent states of obtundation, particularly in the early postoperative setting given the possibility of residual anesthesia.

The RASS[4] will thus be used to assess for agitation (+2 to +4) or sedation (-2 to -5) each timepoint of delirium assessment except for preoperative baseline (where the RASS will not be administered).

Headache

Headache presence and severity will also be assessed (10-centimeter visual analog scale, VAS) at each delirium assessment timepoint. The rationale for this outcome is that perioperative caffeine administration has been demonstrated to reduce rebound headache, particularly in habitual caffeine users.[25,54]

Opioid Consumption

Perioperative opioid consumption will be collected via electronic medical records and converted to oral morphine equivalents as we have previously described.[6]

8.2 SAFETY AND OTHER ASSESSMENTS

The following additional procedures will be conducted to assess for respective safety outcomes and events:

- **Vital signs** (e.g., temperature, pulse, respirations, blood pressure). Vitals will be collected clinically per perioperative standards and protocols. These data will be collected and analyzed in relation to study drug administration, with particular focus on cardiovascular Adverse Events (AEs) (**See Section 9.4.4., Safety Analyses**).
- **Assessment of adverse events.** Assessment for Adverse Events (AEs) will occur throughout the study period (**Section 1.3, Schedule of Activities, SoA)** as described in following sections.
- **Baseline caffeine intake**. Habitual caffeine intake will be assessed among participants and categorized into no daily intake or any daily intake.
- **Baseline cognitive function**. Baseline cognitive function will be assessed via AD8 Dementia Screening Interview, Montreal Cognitive Assessment, and Cognitive Instrumental Activities of Daily Living.
- **Instrumental Activities of Daily Living**. Instrumental Activities of Daily Living will be assessed to determine preoperative functional status.
- **Postoperative nausea and vomiting.** Measured via the Postoperative Nausea and Vomiting Intensity Scale[89] in the PACU, postoperative day one afternoon, and postoperative day two afternoon. Any vomiting and antiemetic use from PACU admission through postoperative day two hours will also be recorded.
- **Arrhythmias.** Any new cardiac arrhythmia not previously experienced by the patient will be reported from PACU admission through postoperative day two.
- **Restraint use.** Any instance of restraint use related to altered mental status will be recorded.
- **Injury to self or others.** Any injury to self or others resulting from agitation/altered mental status
- **Falls.** Fall presence as reported by the patient, hospital staff, or medical record.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

The following guidelines will be used to describe AE severity:

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious."

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.

- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.]

8.3.3.3 EXPECTEDNESS

The Study PI (Vlisides) will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The study team will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

All serious, unexpected, and probably related events must be reported to the study principal investigator, Phillip Vlisides (pvliside@med.umich.edu).

8.3.5 ADVERSE EVENT REPORTING

The study team will report Adverse Events (AEs) per guidelines and timetables set forth by University of Michigan Institutional Review Board (IRBMED). AEs will also be uploaded to the online data repository, the Research Electronic Data Capture (REDCap) system.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The study clinician will immediately report to the sponsor any serious adverse event, whether or not considered study intervention related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Individual participants will be notified of any serious, unanticipated adverse events probably related to study interventions.

8.3.8 EVENTS OF SPECIAL INTEREST

Not applicable

8.3.9 REPORTING OF PREGNANCY

Pregnancy tests will not be ordered for this study, as only patients ≥70 years of age will be eligible.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research (“possibly related” means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEM REPORTING

An investigator shall submit to the sponsor and to the reviewing Institutional Review Board (IRB) a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect (21 CFR 812.150(a)(1)), A sponsor who conducts an evaluation of an unanticipated adverse device effect under 812.46(b) shall report the results of such evaluation to the Food and Drug Administration (FDA) and to all reviewing IRB's and participating investigators within 10 working days after the sponsor first receives

notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests (21 CFR 812.150(b)(1)).

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Participants will be informed of UPs in in accordance with IRB and sponsor recommendations.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- Primary Efficacy Endpoint(s):

  This trial tests the primary hypothesis that intravenous caffeine citrate, administered during surgical closure, and on the first two postoperative mornings, will reduce the incidence of postoperative delirium as identified by the long-form CAM screening tool.[1] The CAM will be complemented by a validated chart review method[65,66] to account for any episodes of delirium for a given day not detected by the in-person CAM assessment.

9.2 SAMPLE SIZE DETERMINATION

Both caffeine groups will be compared to the placebo group based on Generalized Estimating Equation (GEE) modeling. Sample size calculations were thus conducted via GEE Tests for Multiple Proportions in a Cluster-Randomized Design with Power Analysis and Sample Size Software (2022; NCSS, LLC. Kaysville, Utah, USA).[90] Significance level (α) was set at 0.05. A baseline early postoperative delirium incidence (including the PACU timeframe) of 30% was conservatively estimated based on our preliminary trial.[20] A sample size of 250 participants will provide between 80-95% power assuming a baseline delirium incidence of 30%, an incidence ranging between 10-30% in the low-dose group, and an incidence between 10-15% in the high-dose 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%.[20] Increased potency may be expected with older patients given the reduced pharmacologic volume of distribution[74] and a possible age-caffeine interaction effect with respect to cognition.[73] This sample size also accounts for an approximate 10% dropout rate. Lastly, no interim analyses are planned in relation to the primary outcome.

9.3 POPULATIONS FOR ANALYSES

The primary analysis for this study will follow an intention-to-treat approach. That is, patients will be analyzed based on initial group allocation, regardless of protocol deviations (e.g., not receiving the study drug). A secondary, per-protocol approach will then be performed, which will include all randomized participants who received the study drug as intended and with available delirium assessments for each corresponding day.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

For descriptive statistics, categorical outcomes will be presented as proportions (frequencies) and continuous data will be presented as means (±standard deviation) or medians (interquartile range). Normality of distribution will be assessed using the Shapiro-Wilk test, and parametric or non-parametric tests will be applied as appropriate. For statistical modeling, covariates will be specified in the following

sections. All inferential testing will be two-sided, and p-values <0.05 will be considered statistically significant. 95% confidence intervals will be reported.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

As previously described, postoperative delirium will serve as the primary endpoint. The primary analytical test will be a multivariable logistic regression model that will follow the GEE approach. Independent variables will include the placebo group (reference), low-dose caffeine group, high-dose caffeine group, and *a priori* variables that may be independently predictive of delirium (e.g., 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[83]). Baseline cohort imbalances, defined by absolute standardized differences >0.20, will also be included in this model.

Lastly, 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 to results with the actual data in the 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.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

For secondary endpoints, a similar GEE-based approach will be used. Within- and between- group comparisons will be analyzed based on coefficients in the model. This approach also allows for flexibility with missing data. Unstandardized beta coefficients will be presented with 95% confidence intervals and p-values (<0.05 will be considered statistically significant).

For non-repeated continuous measures (e.g., delirium duration, cumulative opioid consumption) and binary outcomes (e.g., postoperative delirium, headache), we will use the same GEE modeling approach. 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, low-dose caffeine group, high-dose). The daily number of caffeinated beverages will be recorded for each participant, and the resulting distribution will be analyzed and used to inform the most appropriate categorization of habitual caffeine users (e.g., non-users, low-dose, high-dose, etc.).

9.4.4 SAFETY ANALYSES

Data will be reported on specific safety outcomes that may be related to caffeine. Despite the high safety profile associated with caffeine, certain risks have been associated with administration (see **Section 2.3, Risk/Benefit Assessment**). The following adverse events that may occur with caffeine will be reported:

Outcome	**Measure**
New cardiac arrhythmia (e.g., supraventricular tachycardia, ventricular tachycardia) incidence	Incidence (%)
SBP (mm Hg)*	n (SD)
DBP (mm Hg)*	n (SD)

HR (BPM)*	n (SD)
Restraint use	Incidence (%)
Injury to self or others	Incidence (%)
Postoperative Nausea and Vomiting**	Score (n)
Dehydration†	Incidence (%)
Allergic Reaction‡	Incidence (%)

**Vitals will be presented as descriptive statistics – no cutoff thresholds will be assigned. **Via Postoperative Nausea and Vomiting Intensity Scale. †Dehydration will be recorded if this term is described in the medical record by clinical teams caring for the patient.* ‡The nature of any suspected allergic reaction will be reported in full detail.

The study drug will be discontinued in the event of new-onset cardiac arrhythmia, suspected allergic reaction, or any other concern raised by either the clinical or research team. Adverse events will otherwise be coded as described in **Section 8.3, Adverse Events and Serious Adverse Events.**

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Study arms will be compared on baseline characteristics, including demographics and medical comorbidities. Absolute standardized differences will be used to compare groups at baseline.

9.4.6 PLANNED INTERIM ANALYSES

No formal interim analyses are planned with respect to intervention efficacy. However, interim safety reviews may be conducted at the discretion of the Data and Safety Monitoring Board (DSMB). Any serious adverse event occurring during the study infusion, that may be related to drug administration, will trigger a stopping of drug administration. Drug infusion may also be stopped at the discretion of the clinical or research team for any additional concern not previously described.

9.4.7 SUB-GROUP ANALYSES

A trial subgroup analysis will be conducted in patients meeting criteria for Mild Cognitive Impairment at preoperative baseline (anticipated n=50)[91] based on preoperative AD8 screening, Montreal Cognitive Assessment score <26, 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 electroencephalographic (EEG) measures.[21,92] As a secondary analysis, we will determine whether caffeine exerts a differential effect on cognitive outcomes in patients with Mild Cognitive Impairment, based on our evidence that caffeine may improve neural criticality, and criticality breakdowns are postulated to underlie Mild Cognitive Impairment and Alzheimer's disease. [21,92,93] Delirium incidence, severity, and Montreal Cognitive Assessment scores one month post-discharge will also be compared in those with and without baseline Mild Cognitive Impairment.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual data will not be tabulated for this study.

9.4.9 EXPLORATORY ANALYSES

As a secondary trial analysis, an additional aim will be to identify the underlying cortical dynamics of postoperative delirium. We will perform advanced EEG analysis with a high-density, whole-scalp system, on all clinical trial patients at preoperative baseline and during postanesthesia care unit (PACU) recovery. A separate, low-density EEG system will be used during each of the first two postoperative mornings. Based on our preliminary data,[21,92] we hypothesize that Deviations from neural criticality, based on EEG-based surrogate markers, will occur during delirium. The impact of caffeine on neural criticality will also be tested, and network-based measures (e.g., global efficiency, hub structure, connection strength, etc.) will also be analyzed.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. Written consent materials are submitted with this protocol.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the investigator, funding agency, the Food and Drug Administration, and other regulatory authorities as needed. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- PI decision
- Sponsor decision
- Regulatory and/or other oversight body decision

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or FDA.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of any biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored on the Research Electronic Data Capture (REDCap) system as managed by the Michigan Institute for Clinical and Health Research. Data stored on REDCap will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. This online database will be password protected and managed on secured serves by the Michigan Institute of Clinical and Health Research. At the end of the study, all study databases will be de-identified and archived.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored in secure, locked offices and storage locations. After the study is completed, the de-identified, archived data will be electronically stored on the Research Electronic Data Capture (REDCap) system, which is managed by the Michigan Institute for Clinical and Health Research protected. Data will be available for use by other researchers including those outside of the study. Permission to store and transmit data to the Michigan Institute for Clinical

and Health Research REDCap server will be included in the written consent. During the conduct of the study, an individual participant can choose to withdraw consent to have data stored for future research.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator
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Additionally, an executive steering committee will (1) serve as an advisory panel to the study PI (Vlisides) and (2) co-host monthly conference calls with the rest of the trial team to review study operations, progress, and issues that may arise. We will seek an Investigational New Drug Exemption from the FDA, as this exemption was approved (#137936) for our previous, preliminary trial (NCT03577730).

10.1.6 SAFETY OVERSIGHT

In conjunction with the National Institute on Aging, an independent Data and Safety Monitoring Board (DSMB) will be commissioned. The DSMB will be composed of individuals with the appropriate expertise who will guide the National Institute on Aging representatives and the study investigators.
The DSMB will be comprised of external members with no direct involvement in the trial.

The DSMB members will have appropriate – and complementary – context expertise (e.g., anesthesiologists, biostatisticians with clinical trials experience, etc.). DSMB members will not have conflicts of interest – financial, proprietary, professional, or otherwise – that could threaten impartial, independent decision-making responsibilities. The DSMB charter will be drafted and approved by all relevant parties, and meetings will occur twice per year. The trial statistician team will be responsible for compiling and curating data into reports for the DSMB.

The DSMB meetings will focus mainly on the following study elements: safety data (e.g., postoperative nausea and vomiting, arrhythmias, falls, etc.), data quality, and enrollment data and projections. The DSMB may consider early study termination based on safety concerns, but there are no plans to terminate the study early based on apparent benefit or futility. Adequate statistical power, with the pre-specified sample size, will be required for the primary analysis along with pre-specified subgroup analyses (e.g., patients with Mild Cognitive Impairment). Early trial termination may result in effect size inflation compared to those not stopped early.[94-96] The effect of caffeine on secondary outcomes (e.g., delirium severity, quality of recovery, etc.) is also important, and early termination would attenuate these analyses. As such, there will be no plan for early trial termination based on perceived efficacy or futility with respect to the primary outcome of delirium.

Lastly, the DSMB will hold both open and closed sessions. Open sessions will focus on overall status of the trial, pooled data analysis, and overarching concerns (e.g., enrollment, data quality). The objective of the closed sessions will be to review safety data, effectiveness outcomes, and adverse events, in an unblinded manner.

10.1.7 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

Clinical site monitoring will be performed by the Study Monitoring team of the Michigan Institute for Clinical and Health Research. This team will perform independent audits of trial operations, including initiation, interim, and close-out visits. The monitoring plan will focus on protocol and regulatory adherence, maintenance of essential documentation, and appropriate storage and accountability of the study drug. Reports will then be made available to the study team, IRB, and DSMB.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Dr. Vlisides (PI) and Ms. Amy McKinney (Project Manager) will be responsible for coordinating the collection of data, performing data cleaning, monitoring data accuracy and completeness, ensuring regulatory compliance (trial registration and DSMB coordination), generating data reports throughout the trial lifespan, and analyzing the data in conjunction with the statistician team. Dr. Vlisides will also supervise the team of research assistants, in conjunction with Ms. Amy McKinney, to ensure proper data collection and management per study protocols. The study team will provide direct access to source data/documents and reports for the purpose of monitoring and auditing by the sponsor and inspection by local and regulatory authorities.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

Quality control (QC) procedures will also be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. The Michigan Institute of Clinical and Health Research also performs routine, scheduled maintenance and QC checks on the REDCap system. The REDCap system incorporates logic that requires appropriate responses, and missing/incorrect data are readily and transparently highlighted. Any missing data or data anomalies will be communicated directly to Dr. Vlisides and Ms. McKinney.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the study PI (Vlisides). The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report

form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into REDCap, a 21 CFR Part 11-compliant data capture system provided by the Michigan Institute for Clinical and Health Research. REDCap resides on a secured, password-protected online network. The data system also includes password protection, audit trails, automated export procedures for downloads to various statistical packages, and procedures for importing data from various external sources. Data will be entered directly from the source documents.

10.1.9.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of three years. However, these documents may be retained for a longer period if required by local regulations.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within seven working days of identification of the protocol deviation, or within seven working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to funding agencies, and reported to Program Official and the coordinating center (University of Michigan). Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-

reviewed journals. Data from this study may be requested from other researchers 2 years after the completion of the primary endpoint by contacting the study PI (Vlisides).

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

10.2 ADDITIONAL CONSIDERATIONS

Not applicable.

10.3 ABBREVIATIONS

AE	Adverse Event
CFR	Code of Federal Regulations
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
IND	Investigational New Drug Application
IRB	Institutional Review Board
MOP	Manual of Procedures
NCT	National Clinical Trial
NIH	National Institutes of Health
PACU	Postanesthesia Care Unit
PI	Principal Investigator
QoR	Quality of Recovery Scale
QC	Quality Control
SAE	Serious Adverse Event
SOA	Schedule of Activities
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
1.0	5-9-2022	Initial protocol drafted	
2.0	12-14-2022	Expanded delirium assessment timeframe through the first three postoperative days	To test durability of delirium prevention with caffeine by assessing for delirium 24+ hours after the final caffeine dose. Amendment approval date 2/22/2023.
2.0	12-14-2022	Modified the eligibility criteria to include anticipated length of stay 72 hours to account for a third day of postoperative delirium testing	See above. Amendment approval date 2/22/2023.

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Caffeine, Postoperative Delirium, And Change In Outcomes after Surgery (CAPACHINOS)-2: Protocol for a Randomised Controlled Trial

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

Section/item	ItemNo	Description	Page Number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4, 20, Table 3
	2b	All items from the World Health Organization Trial Registration Data Set	This information is available on the ClinicalTrials.gov registry.
Protocol version	3	Date and version identifier	Supplemental online appendix 1
Funding	4	Sources and types of financial, material, and other support	30 (within manuscript file)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	30 within manuscript file)

	5b	Name and contact information for the trial sponsor	Online supplemental appendix 1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	30
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	17-18, Methods and Analysis, Data and Safety Monitoring
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6, Table 1
	6b	Explanation for choice of comparators	9, 10 (Methods and Analysis, Interventions)
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8 (Methods and Analysis, Trial Overview and Design)
Methods: Participants, interventions, and outcomes			

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8 (Methods and Analysis, Trial Overview and Design)
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	9 (Methods and Analysis, Eligibility Criteria)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-10 (Methods and analysis, Interventions)
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	11 (Methods and Analysis, Interventions)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Online supplemental appendix 1 (Section 6.4. Study Intervention Compliance)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Supplemental online appendix 1 (Section 6.5. Concomitant Therapy)

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11-13 (Methods and Analysis, Outcomes)
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 2, Online supplemental appendix (Section 1.3. Schedule of Activities)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15-16, (Methods and Analysis, Sample Size and Power Calculations)
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Supplemental online appendix 1 (Section 5.5. Strategies for Recruitment and Retention)
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8 (Methods and analysis, trial overview and design)

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8 (Methods and Analysis, Trial Overview and Design) – managed by research pharmacy
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8 (Methods and Analysis, Trial Overview and Design)
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8 (Methods and Analysis, Trial Overview and Design)
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Supplemental online appendix 1. 10.1.6 Safety Oversight.
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11-13 (Methods and Analysis), supplemental online appendix 1 – sections 1.3 (schedule of activities), 3 (Objectives and endpoints), 10.1.9 (Data handling and record keeping)
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Online supplemental appendix 1, Section 5.5. Strategies for Recruitment and Retention
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13 (Methods and Analysis, Data Management)
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14-17 (Methods and Analysis, Statistical Analysis sections)
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16-17 Methods and analysis, prespecified substudy and subgroup analyses section)

	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14-15 (Methods and Analysis, Statistical Analysis sections)
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	17-18 (Data and safety monitoring section)
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	17-18 (Data and Safety Monitoring section). Additional DSMB information also provided in Supplemental online appendix 1.
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	17-88 (Data and Safety Monitoring section). Additional information provided in Supplemental online appendix 1 – Section 8.3. Adverse events and serious adverse events
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13 (Data Management)

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	4 (Abstract), 8 (Methods and Analysis, Trial Overview and Design)
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	8 (Methods and analysis, Trial Overview and Design)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8 (Methods and analysis, Trial Overview and Design)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	8 (Methods and analysis, Trial Overview and Design)
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Online supplemental appendix 1 – 10.1.3 Confidentiality and Privacy
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	30 (manuscript submission file)

Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	N/A
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A (harm/compensation descriptions are outlined in the written consent form).
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	19-20 (Ethics and dissemination), online supplemental appendix (section 10.1.11)
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Online supplemental appendix (section 10.1.11)
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Will be uploaded to the ClinicalTrials.gov registry site.
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Online supplemental appendix (section 10.1.4).

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

UNIVERSITY OF MICHIGAN
CONSENT TO BE PART OF A RESEARCH STUDY

1. KEY INFORMATION ABOUT THE RESEARCHERS AND THIS STUDY

Study title: The Caffeine, Postoperative Delirium, and Change in Outcomes After Surgery (CAPACHINOS-2) Study

Company or agency sponsoring the study: National Institute on Aging (NIA) – National Institutes of Health (NIH)

Names, degrees, and affiliations of the principal investigator and study coordinator (if applicable):

Principal Investigator: Phillip Vlisides, MD, Department of Anesthesiology, University of Michigan
Study Coordinator: Amy McKinney, MA, Department of Anesthesiology, University of Michigan

1.1 Key Study Information

You may be eligible to take part in a research study. This form contains important information that will help you decide whether to join the study. Take the time to carefully review this information. You should talk to the researchers about the study and ask them any questions you have. You may also wish to talk to others such as your family, friends, or other doctors about joining this study. If you decide to join the study, you will be asked to sign this form before you can start study-related activities. Before you do, be sure you understand what the research study is about.

A research study is different from the regular medical care you receive from your doctor. Research studies hope to make discoveries and learn new information about diseases and how to treat them. You should consider the reasons why you might want to join a research study or why it is not the best decision for you at this time.

Research studies do not always offer the possibility of treating your disease or condition. Research studies also have different kinds of risks and risk levels, depending on the type of the study. You may also need to think about other requirements for being in the study. In your decision to participate in this study, consider all of these matters carefully.

Study Drug:
Caffeine citrate is an FDA-approved drug. However, it is not approved for how it's being tested in this study.

Randomization:
This study involves a process called randomization. This means that the dosage of Caffeine citrate or placebo (dextrose 5% in water) you receive in the study is not chosen by you or the researcher. The study design divides study participants into separate groups, based on chance (like the flip of a coin), to

compare different treatments or procedures. If you decide to be in the study, you need to be comfortable not knowing which study group you will be in.

There can be risks associated with joining any research study. The type of risk may impact whether you decide to join the study. For this study, some of these risks may include anxiety, irritability, increased use of pain medication, gastrointestinal distress, tremors, nervousness, and sleep disruption. More detailed information will be provided later in this document.

This study may offer some benefit to you now, including improved cognitive function (e.g., thinking, memory, attention), reduced headache, improved overall quality of recovery, and faster wake-up time from surgery (anesthetic emergence). The results of this study may help future surgical patients recover from surgery. It is also possible that you may not benefit from participating in this research study.

We expect the amount of time you will participate in this study will include the day of surgery, the first three following surgery, and then a final study visit (which can be completed via phone or video conference) 30 days after surgery.

You can decide not to be in this study. Participation is completely voluntary.

Even if you decide to join the study now, you are free to leave at any time if you change your mind.

More information about this study continues in Section 2 of this document.

2. PURPOSE OF THIS STUDY

2.1 Study purpose:

Many patients experience brain dysfunction (delirium or confusion) after surgery. Caffeine citrate is an FDA-approved drug. However, it is not approved for how it's being tested in this study, as it is not approved for brain recovery after surgery. Research evidence suggests that caffeine, a drug normally found in coffee and soda, may improve cognition (i.e., thinking and memory) and headache immediately following surgery. Caffeine has also been found to improve cognitive function (e.g., memory, attention) and mood in a variety of settings. **Thus, the purpose of this study is to see if caffeine citrate given before patients wake-up from surgery, and given for the first two days following surgery, may improve brain function and overall quality of recovery after surgery**. We are also testing to see if caffeine speeds wake-up time from anesthesia.

3. WHO MAY PARTICIPATE IN THE STUDY

Taking part in this study is completely **voluntary**. You do not have to participate if you don't want to. You may also leave the study at any time. If you leave the study before it is finished, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled.

3.1 Who can take part in this study?

In order to be eligible to participate in this study, you must meet all of the following criteria:

1. Must be able to provide informed consent.
2. Stated willingness to comply with all study procedures and availability for the duration of the study.
3. Male or female, ≥70 years of age
4. Presenting for non-cardiac surgery, non-intracranial neurologic, non-major vascular (e.g., operations below the diaphragm) surgery with planned admission for at least 48 hours.

If you meet any of the following criteria you will be excluded from participation in this study:

1. Emergency surgery
2. Outpatient surgery
3. Severe cognitive impairment precluding the capacity for informed consent
4. Seizure disorder history
5. Intolerance or allergy to caffeine (based on subjective reporting or objective documentation)
6. Weight >130 kg (as a 3 mg/kg dose would approach the upper limit of daily intake recommended by the FDA)
7. Enrollment in conflicting research study
8. Patients in acute liver failure
9. Acute kidney injury preoperatively
10. Diagnosis of pheochromocytoma
11. Severe audiovisual impairment
12. Non-English speaking

3.2 How many people are expected to take part in this study?

A total of 250 patients are expected to take part in this study, all here at the University of Michigan.

4. INFORMATION ABOUT STUDY PARTICIPATION

4.1 What will happen to me in this study?

Baseline or initial assessment:

After enrollment, you will undergo screening for eligibility by trained research members. Baseline vitals, including height, weight, heart rate, heart rhythm, and blood pressure will be taken and a physical exam will be performed by clinic and perioperative clinicians per clinical standards. Baseline assessments will be completed, including a delirium or confusion assessment and cognitive assessment independent daily living activities scale, and a dementia screening form. Study screening forms will be reviewed by the Study PI anytime between the initial screening visit and surgical intervention.

Day of Surgery:

On the day of your surgery, an electroencephalogram (EEG) cap will be placed on your head, which is a device that detects electrical activity in the brain. This cap has small, flat plastic discs that are placed on the scalp. The research team will use this cap to monitor brainwave activity during and immediately after surgery; this will help us to determine if caffeine speeds wake-up time from anesthesia. Towards the end of your surgery, you will be given either caffeine or placebo through your IV, and both your clinical and research teams will continue to monitor you during this time.

Randomization, Dosing, and Administration:

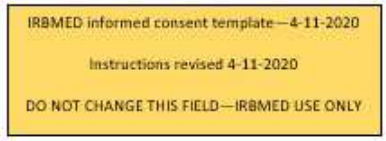
The study design divides study participants into separate groups, based on chance (like the flip of a coin), to compare different treatments or procedures. If you decide to be in the study, you need to be comfortable not knowing which study group you will be in. For some research studies such as the one you are being asked to join, it is important that you do not learn which dose you received during the study. Whether you intend to or not, sometimes learning this information may make you change your actions and behaviors in ways that could impact the outcome of the study. You will be randomized with a 1:1:1 (one-in-three) chance to receive one of the following study doses via IV infusion during your scheduled surgery and for the first two mornings after surgery:

-Placebo (Dextrose)
-Caffeine 1.5 mg/kg (low dose) – same amount as approximately one cup of coffee
-Caffeine 3 mg/kg (high dose) – same amount as approximately two cups of coffee

Shortly after arrival in the recovery room, the EEG cap will be removed after final data are collected. Once you are awake and ready, we will briefly check for signs of confusion and ask about pain, including headache. Your vital signs will be taken by your clinical care team.

Days 1 and 2 After Surgery:

For the next two postoperative mornings, study drug will be given via IV infusion with your scheduled, morning medications which the research nurse or physician assistant will oversee. Your vital signs will be taken by your clinical care team and recorded for study purposes. During drug administration, we will place small EEG stickers on your forehead for monitoring electrical activity of the brain.



Consent Subtitle: _____
Consent Version: _____

As a subject participating in this research study, you have certain responsibilities that may apply to this study, including taking your study medications as directed and reporting any adverse reactions you may have during the study.

Our research team will visit you briefly twice daily, for the first 3 days after surgery, to check for signs of delirium, pain, headache, and overall recovery. On the third day, we will ask you to complete a brief survey regarding your quality of recovery.

30 Days after Surgery:
One month after surgery, we schedule a brief follow-up meeting, via phone or video conference, to briefly ask about your health. After this, your study participation will end. Your medical record will be reviewed for up to 30 days following your surgery.

UNSPECIFIED FUTURE USE OF EEG DATA:

We would also like your permission to study your EEG results for future, unspecified research. The future research may be similar to this study or may be completely different. You can take part in this study even if you decide not to let us analyze your EEG results for future studies. **If you give us your permission, we will use your EEG data and medical information for future research.**

Even if you give us permission now to keep some of your EEG data and medical information, you can change your mind later and ask us to destroy it. Keep in mind, however, that once we have analyzed your EEG data, we may not be able to take the information out of our research.

Additional risks of this sub-study may include a very small risk of loss of confidentiality. Your data will be stored at the University of Michigan Medical School, where only study team members will have access to your coded data. That is, your name and medical record number will be removed from this data, and only an assigned code will remain on it. Your EEG data will not be shared with anyone outside of our research team at the University of Michigan.

You will not find out the results of future research on your EEG results. Allowing us to do future research on your EEG results and medical information will not benefit you directly. Any findings we discover will not be used for your clinical care. These findings will only be used for discovery of information purposes (research) only.

No parties can financially benefit from this additional sub-study.

4.2 How much of my time will be needed to take part in this study?

Baseline or initial assessment: approximately **20 minutes** to learn about the study, sign the consent form, and perform our baseline assessments.

Day of Surgery: approximately **10 minutes** before surgery to place our EEG cap. In the recovery unit an additional **10 minutes** to perform our after-surgery assessments. We will give you the IV caffeine or placebo during your surgery, so this will not take any more time.

Days 1 and 2 after Surgery: the study drug will be given via IV infusion with scheduled, morning medications as administered and overseen by the research nurse or physician assistant; **this will take approximately 30 minutes.**

It will take approximately **5 minutes** each day to ask you about your pain levels, and feelings of confusion. On the second day, we will ask you to complete a brief survey regarding your quality of recovery; this survey may take up to **5 minutes**.

Day 3 after Surgery: It will take approximately **5 minutes** each day to ask you about your pain levels, and feelings of confusion. On the third day, we will ask you to complete a brief survey regarding your quality of recovery; this survey may take up to **5 minutes**.

30 Days after Surgery:
One month after surgery, we will briefly meet with you via phone or video conference; this may take up to **15 minutes**.

4.3 When will my participation in the study be over?
Your participation will officially be over **30 days after your surgery upon completion of the follow-up visit**. We may review your chart after this period to review data and assess for any changes in your health that may relate to this research study.

4.4 What will happen with my information used in this study?
With appropriate permissions, your biospecimens and collected information may also be shared with other researchers, here, around the world, and with companies.

Your identifiable private information may be stripped of identifiers and used for future research studies or distributed to another researcher for future research studies without additional informed consent.

5. INFORMATION ABOUT STUDY RISKS AND BENEFITS

5.1 What risks will I face by taking part in the study? What will the researchers do to protect me against these risks?
The known or expected risks are outlined below:

If you have a condition that makes caffeine high-risk for you we will not enroll you in this study, this will make significant side effects very unlikely. Mild side effects (1-10%), such as flushing, jitters, nausea, and irritability, are short lasting. Patients receiving caffeine may also use additional pain medication during early recovery after surgery, which may be due to being more awake, alert, and able to effectively communicate pain to nurses and doctors. More serious side effects (<1%), such as irregular heartbeats and seizures, are highly unlikely with the amount of caffeine used in this study. Furthermore, patients with history of seizures will not be enrolled in this study as previously discussed. You will also be

monitored per our standard clinical guidelines before, during, and after surgery. If any harmful side effects are noted or suspected, the caffeine will be stopped immediately.

The risk associated with having the EEG electrodes placed is minimal and include the potential for slight irritation to the skin (scalp). This irritation will resolve on its own. Rarely, there is possible risk of an allergic reaction to any medical adhesive or gel material, such as those used in this study, but our team aggressively screens for any previously known allergies to these types of materials.

We believe there are no known risks associated with performing cognitive assessments. It is possible that you may feel inconvenienced or frustrated by them, in which case you can stop at any time.

There is also a minimal risk of loss of confidentiality. We will minimize this risk by utilizing an indirect data link, which will not personally identify you. The only persons who will be able to break the indirect data link are the researchers conducting this study.

As with any research study, there may be additional risks that are unknown or unexpected.

5.2 What happens if I get hurt, become sick, or have other problems as a result of this research?
The researchers have taken steps to minimize the risks of this study. Even so, you may still have problems or side effects, even when the researchers are careful to avoid them. Please tell the researchers listed in Section 10 about any injuries, side effects, or other problems that you have during this study. You should also tell your regular doctors**.** As mentioned, you will be monitored by both your regular clinical team along with the research team during the caffeine administration. If any harmful side effects are suspected, we will stop giving the caffeine immediately.

5.3 If I take part in this study, can I also participate in other studies?
Being in more than one research study at the same time, or even at different times, may increase the risks to you. It may also affect the results of the studies. You should not take part in more than one study without approval from the researchers involved in each study.

5.4 How could I benefit if I take part in this study? How could others benefit?
This study may offer some benefit to you now, including reduced confusion after surgery, improved cognitive function (e.g., thinking, memory), reduced headache pain, and faster wake-up time from surgery (anesthetic emergence). The results of this study may help future surgical patients recover from surgery. It is also possible that you may not benefit from participating in this research study.

5.5 Will the researchers tell me if they learn of new information that could change my willingness to stay in this study?
Yes, the researchers will tell you if they learn of important new information that may change your willingness to stay in this study. If new information is provided to you after you have joined the study, it is possible that you may be asked to sign a new consent form that includes the new information.

6. ALTERNATIVES TO PARTICIPATING IN THE STUDY

6.1 If I decide not to take part in this study, what other options do I have?

Participating in this study is completely voluntary. You may choose not to participate. In this event, your medical care will proceed as it routinely would otherwise.

7. ENDING THE STUDY

7.1 If I want to stop participating in the study, what should I do?
You are free to leave the study at any time. If you leave the study before it is finished, there will be no penalty to you. You will not lose any benefits to which you may otherwise be entitled. If you choose to tell the researchers why you are leaving the study, your reasons for leaving may be kept as part of the study record. If you decide to leave the study before it is finished, please tell one of the persons listed in Section 10 "Contact Information".

7.2 Could there be any harm to me if I decide to leave the study before it is finished?
No.

7.3 Could the researchers take me out of the study even if I want to continue to participate?
Yes. There are many reasons why the researchers may need to end your participation in the study. Some examples are:

- The researcher believes that it is not in your best interest to stay in the study.
- You become ineligible to participate.
- Your condition changes and you need treatment that is not allowed while you are taking part in the study.
- You do not follow instructions from the researchers.
- The study is suspended or canceled.

8. FINANCIAL INFORMATION

8.1 Who will pay for the costs of the study? Will I or my health plan be billed for any costs of the study?

The study will pay for research-related items or services that are provided only because you are in the study. If you are not sure what these are, see Section 4.1 above or ask the researchers for a list. If you get a bill you think is wrong, call the researcher's telephone number listed in Section 10.1.

You or your health plan will pay for all the things you would have paid for even if you were not in the study, like:

- Health care given during the study as part of your regular care
- Items or services needed to give you study drugs or devices
- Monitoring for side effects or other problems
- Deductibles or co-pays for these items or services.

If you do not have a health plan, or if you think your health plan may not cover these costs during the study, please talk to the researchers listed in Section 10 below or call your health plan's medical reviewer.
By signing this form, you do not give up your right to seek payment if you are harmed as a result of being in this study.

8.2 Will I be paid or given anything for taking part in this study?
No.

8.3 Who could profit or financially benefit from the study results?
No party will profit or financially benefit from these study results. Research can lead to new discoveries, such as new tests, drugs, or devices. Researchers, their organizations, and other entities, including companies, may potentially benefit from the use of the data or discoveries. You will not have rights to these discoveries or any proceeds from them.

9. CONFIDENTIALITY OF SUBJECT RECORDS AND AUTHORIZATION TO RELEASE YOUR PROTECTED HEALTH INFORMATION

The information below describes how the confidentiality of your research records will be protected in this study, and any sub-studies described in this document.

9.1 How will the researchers protect my information?

All measures will be taken to protect your privacy. All of your information will be stored on password protected computer files and only members of the research team will have access to this information. In addition, your information will not be linked directly to your name, but rather indirectly by a random number scheme. Only the study team will have access to the key that allows your name to be determined from the random number that was assigned to you. Also, all members of the research study team are trained and certified in human subject's privacy.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation by the National Institutes of Health which is funding this project or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.

The Certificate of Confidentiality will not be used to prevent disclosure as required by federal, state, or local law of [list what will be reported, such as child abuse and neglect, or harm to self or others].

The Certificate of Confidentiality will not be used to prevent disclosure for any purpose you have consented to in this informed consent document.

A description of this clinical trial will be available on http://www.clinicaltrials.gov/, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

9.2 What protected health information (PHI) about me could be seen by the researchers or by other people? Why? Who might see it?

Signing this form gives the researchers your permission to obtain, use, and share information about you for this study, and is required in order for you to take part in the study. Medical information and billing records are protected by the privacy regulations of the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA). This type of information is called protected health information (PHI). PHI about you may be obtained from any hospital, doctor, and other health care provider involved in your care, including:

- Hospital/doctor's office records, including test results (X-rays, blood tests, urine tests, etc.)
- All records relating to your condition, the treatment you have received, and your response to the treatment
- Billing information
- Demographic information
- Personal identifiers

There are many reasons why information about you may be used or seen by the researchers or others during or after this study. Examples include:

- The researchers may need the information to make sure you can take part in the study.
- The researchers may need the information to check your test results or look for side effects.
- University, Food and Drug Administration (FDA) and/or other government officials, auditors, and/or the IRB may need the information to make sure that the study is done in a safe and proper manner.
- Study sponsors or funders, or safety monitors or committees, may need the information to:
  - Make sure the study is done safely and properly
  - Learn more about side effects
  - Analyze the results of the study
- Insurance companies or other organizations may need the information in order to pay your medical bills or other costs of your participation in the study.

- The researchers may need to use the information to create a databank of information about your condition or its treatment.
- Information about your study participation may be included in your regular UMHS medical record. Federal or State law may require the study team to give information to government agencies. For example, to prevent harm to you or others, or for public health reasons.

The results of this study could be published in an article but would not include any information that would let others know who you are.

9.3 What happens to information about me after the study is over or if I cancel my permission to use my PHI?

As a rule, the researchers will not continue to use or disclose information about you, but will keep it secure until it is destroyed. Sometimes, it may be necessary for information about you to continue to be used or disclosed, even after you have canceled your permission or the study is over.

Examples of reasons for this include:
- To avoid losing study results that have already included your information
- To provide limited information for research, education, or other activities. (This information would not include your name, social security number, or anything else that could let others know who you are.)
- To help University and government officials make sure that the study was conducted properly

As long as your information is kept within the University of Michigan Health System, it is protected by the Health System's privacy policies. For more information about these policies, ask for a copy of the University of Michigan "Notice of Privacy Practices". This information is also available on the web at http://www.uofmhealth.org/patient+and+visitor+guide/hipaa. Note that once your information has been shared with others as described under Question 9.2, it may no longer be protected by the privacy regulations of the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA).

9.4 When does my permission to use my PHI expire?
Your permission expires at the end of the study, unless you cancel it sooner. You may cancel your permission at any time by writing to the researchers listed in Section 10 "Contact Information" (below). If you withdraw your permission, you may no longer be eligible to participate in this study.

10. CONTACT INFORMATION

10.1 Who can I contact about this study?

Please contact the researchers listed below to:
- Obtain more information about the study
- Ask a question about the study procedures or treatments
- Talk about study-related costs to you or your health plan
- Report an illness, injury, or other problem (you may also need to tell your regular doctors)
- Leave the study before it is finished
- Express a concern about the study

Principal Investigator: Phillip Vlisides, MD
Mailing Address: 1500 East Medical Center Drive
1H247 University Hospital
Ann Arbor, MI 48109-5048
Telephone: (734) 936-4270

Study Coordinator: Amy McKinney, MA
Mailing Address: 1500 East Medical Center Drive
F3842 UH-South
Telephone: (734) 647-8129
Email address: adrongo@med.umich.edu

You may also express a question or concern about a study by contacting the Institutional Review Board listed below:

University of Michigan Medical School Institutional Review Board (IRBMED)
2800 Plymouth Road
Building 520, Room 3214
Ann Arbor, MI 48109-2800
Telephone: 734-763-4768 (For International Studies, include the appropriate calling codes.)
Fax: 734-763-1234
e-mail: irbmed@umich.edu

If you are concerned about a possible violation of your privacy or concerned about a study you may contact the University of Michigan Health System Compliance Help Line at 1-866-990-0111.
When you call or write about a concern, please provide as much information as possible, including the name of the researcher, the IRBMED number (at the top of this form), and details about the problem. This will help University officials to look into your concern. When reporting a concern, you do not have to give your name unless you want to.

11. RECORD OF INFORMATION PROVIDED

11.1 What documents will be given to me?

You will receive a copy of the signed and dated informed consent.

12. SIGNATURES

Consent to Participate in the Research Study

I understand the information printed on this form. I have discussed this study, its risks and potential benefits, and my other choices with Dr. Vlisides' designee. My questions so far have been answered. I understand that if I have more questions or concerns about the study or my participation as a research subject, I may contact one of the people listed in Section 10 (above). I understand that I will receive a copy of this form at the time I sign it and later upon request. I understand that if my ability to consent or assent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

Print Legal Name: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

Consent for Participating in an Optional Sub-Study:

This project involves optional participation in a sub-study. I understand that it is my choice whether or not to take part in the sub-study. I understand that if my ability to consent or assent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

_____ Yes, I agree to take part in the optional sub-study.

_____ No, I do not agree to take part in the optional sub-study.

Print Legal Name: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

Principal Investigator's Designee:

I have provided this participant and/or his/her legally authorized representative(s) with information about this study that I believe to be accurate and complete. The participant and/or his/her legally authorized representative(s) indicated that he or she understands the nature of the study, including risks and benefits of participating.

Printed Legal Name: _____

Title: _____

Signature: _____

Date of Signature (mm/dd/yy): _____