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.

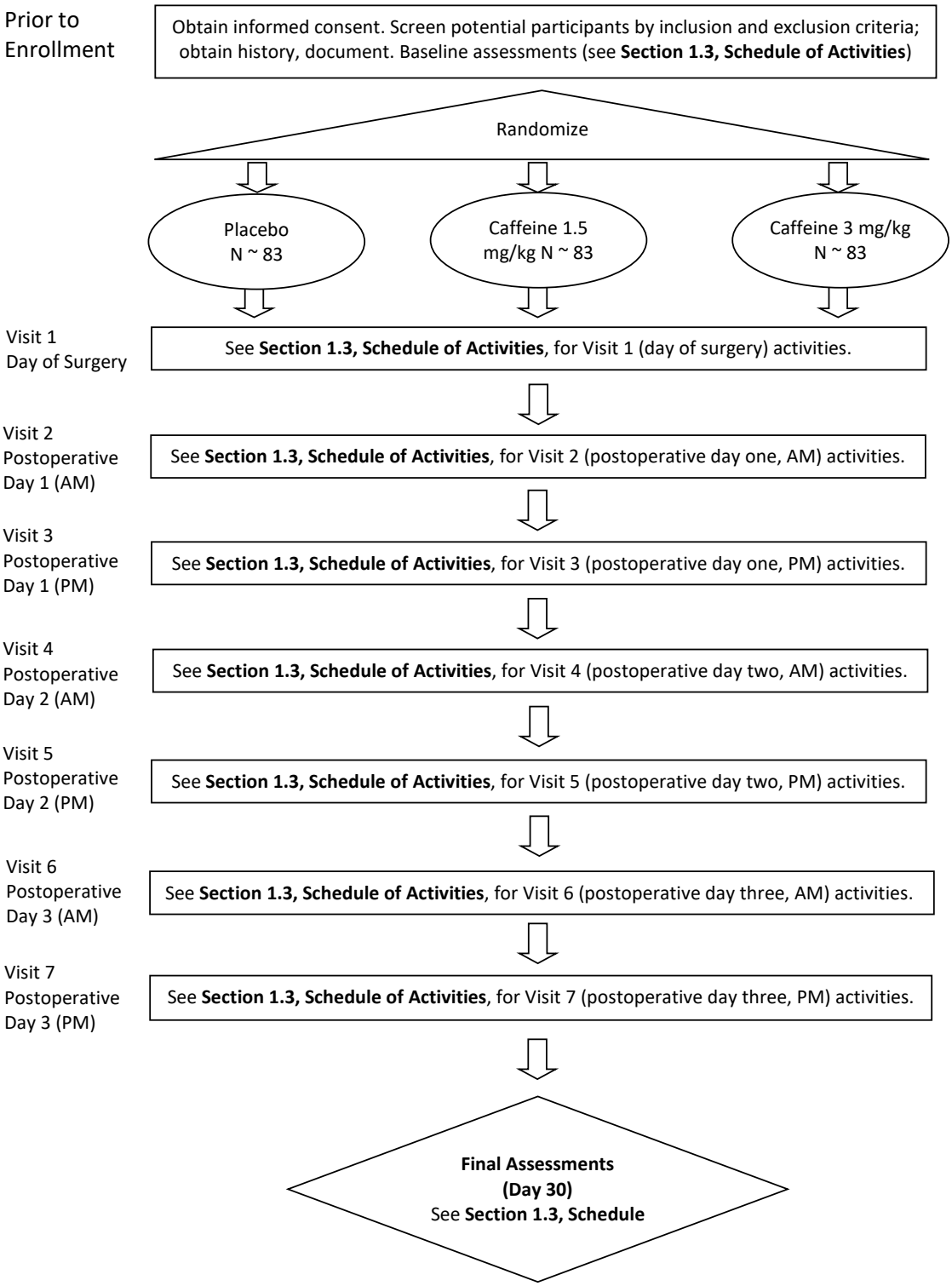
1 PROTOCOL SUMMARY

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

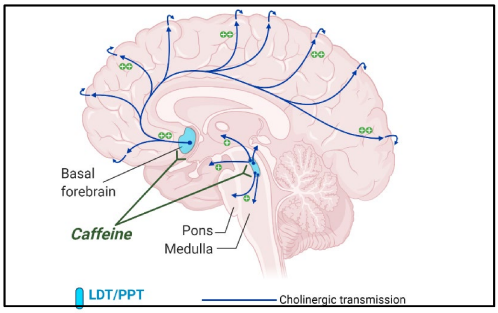


Fig. 1. Caffeine increases cholinergic output from the basal forebrain and lateraldorsal tegmentum and pedunculopontine tegmentum *via* adenosine receptor antagonism. Increased cortical cholinergic tone leads to arousal and improved cognitive function.

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.

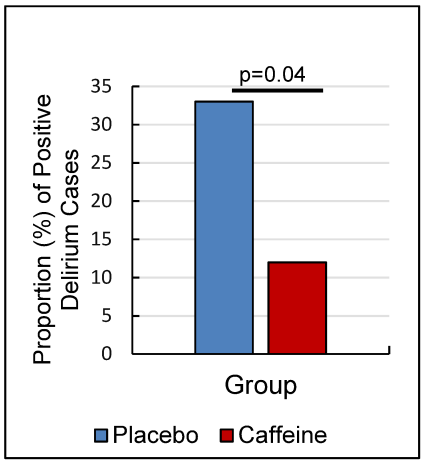


Fig. 2. PACU delirium was significantly reduced in patients receiving intravenous caffeine (4/33, 12%) compared to placebo (10/30, 33%; p=0.04) during surgical closure.

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

The CAffeine, Postoperative Delirium, And CHange IN Outcomes after Surgery-2 (CAPACHINOS-2) Study Protocol <2.0>

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<14 December 2022>

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

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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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