UNIVERSITY OF MICHIGAN
CONSENT TO BE PART OF A RESEARCH STUDY

1. KEY INFORMATION ABOUT THE RESEARCHERS AND THIS STUDY

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

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

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

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

Consent Subtitle: _____
Consent Version: _____

2. PURPOSE OF THIS STUDY

2.1 Study purpose:

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

3. WHO MAY PARTICIPATE IN THE STUDY

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

3.1 Who can take part in this study?

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

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

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

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

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

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

4. INFORMATION ABOUT STUDY PARTICIPATION

4.1 What will happen to me in this study?

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

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

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

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

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

Days 1 and 2 After Surgery:
For the next two postoperative mornings, study drug will be given via IV infusion with your scheduled, morning medications which the research nurse or physician assistant will oversee. Your vital signs will be taken by your clinical care team and recorded for study purposes.

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

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

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

UNSPECIFIED FUTURE USE OF EEG DATA:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

5. INFORMATION ABOUT STUDY RISKS AND BENEFITS

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

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

The risk associated with having the EEG electrodes placed is minimal and include the potential for slight irritation to the skin (scalp). This irritation will resolve on its own. Rarely, there is possible risk of an

allergic reaction to any medical adhesive or gel material, such as those used in this study, but our team aggressively screens for any previously known allergies to these types of materials.

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

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

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

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

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

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

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

6. ALTERNATIVES TO PARTICIPATING IN THE STUDY

6.1 If I decide not to take part in this study, what other options do I have?
Participating in this study is completely voluntary. You may choose not to participate. In this event, your medical care will proceed as it routinely would otherwise.

7. ENDING THE STUDY

7.1 If I want to stop participating in the study, what should I do?

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

7.2 Could there be any harm to me if I decide to leave the study before it is finished?

No.

7.3 Could the researchers take me out of the study even if I want to continue to participate?

Yes. There are many reasons why the researchers may need to end your participation in the study. Some examples are:

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

8. FINANCIAL INFORMATION

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

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

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

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

If you do not have a health plan, or if you think your health plan may not cover these costs during the study, please talk to the researchers listed in Section 10 below or call your health plan's medical reviewer.

By signing this form, you do not give up your right to seek payment if you are harmed as a result of being in this study.

8.2 Will I be paid or given anything for taking part in this study?

No.

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

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

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

9.1 How will the researchers protect my information?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Examples of reasons for this include:

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

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

9.4 When does my permission to use my PHI expire?

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

10. CONTACT INFORMATION

10.1 Who can I contact about this study?

Please contact the researchers listed below to:

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

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

Study Coordinator: Amy McKinney, MA

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

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

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

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

11. RECORD OF INFORMATION PROVIDED

11.1 What documents will be given to me?

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

12. SIGNATURES

Consent to Participate in the Research Study

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

Print Legal Name: _____

Signature: _____

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

Consent for Participating in an Optional Sub-Study:

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

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

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

Print Legal Name: _____

Signature: _____

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

Principal Investigator's Designee:

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

Printed Legal Name: _____

Title: _____

Signature: _____

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