Partners HealthCare System
Research Consent Form

Subject Identification

Certificate of Confidentiality Template
Version Date: January 2018

Protocol Title: Electroencephalogram Studies of Induction and Recovery from Ketamine-Induced General Anesthesia

Principal Investigator: Oluwaseun Johnson-Akeju, M.D., M.M.Sc

Site Principal Investigator:

Description of Subject Population: 15 healthy male and female subjects, ages 18-45 years. American Society of Anesthesiologists (ASA) physical status classification P1.

About this consent form

Please read this form carefully. It tells you important information about a research study. A member of our research team will also talk to you about taking part in this research study. People who agree to take part in research studies are called "subjects." This term will be used throughout this consent form.

Partners HealthCare System is made up of Partners hospitals, health care providers, and researchers. In the rest of this consent form, we refer to the Partners system simply as "Partners."

If you have any questions about the research or about this form, please ask us. Taking part in this research study is up to you. If you decide to take part in this research study, you must sign this form to show that you want to take part. We will give you a signed copy of this form to keep.

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.

Why is this research study being done?

We are doing this research study to find out how and where ketamine acts in the brain. Ketamine is an anesthetic (a drug or agent used to decrease or eliminate the feeling of pain by putting you in an unconscious state).

We will look at your brain using a machine that records your brain's electrical activity, called an electroencephalogram (EEG). EEG is a routine test done at the hospital.

The U.S. Food and Drug Administration (FDA) has approved ketamine for general anesthesia (loss of consciousness) before and during surgery. During this research study, you will receive ketamine at a high enough dose to induce general anesthesia (make you "fall asleep"). We are asking you to take part because you are a healthy adult and are not currently taking medicines that affect brain function. We expect to enroll 15 people in this research study at Massachusetts General Hospital (MGH).

Conflict of Interest Disclosure

Dr. Johnson-Akeju, an investigator on this study, is an inventor of technology that is used in this study. The hospital owns this technology and therefore Dr. Johnson-Akeju and the hospital may benefit financially if this study shows that the technology is valuable. The hospital's conflict of interest policies are handled by the hospital's owner, Partners HealthCare. In accordance with these policies, Partners has determined that the interests create no significant risk to the welfare of participants in this study or to the integrity of the research. If you want more information about this, please contact the Partners Office for Interactions with Industry at 857-282-2024.

How long will I take part in this research study?

It will take you up to 2 weeks to complete this research study. During this time, we will ask you to make 2 visits to the MGH. The first visit will last approximately 3 to 5 hours while the second visit will last approximately 3 hours. The visits will take place at the MGH main campus.

What will happen in this research study?

If you choose to take part in this study, we will ask you to sign this consent form before we do any study procedures.

Study Visit 1 – Screening
The Screening Visit will take about 3 to 5 hours. This visit will take place at the MGH main campus.

During this visit, we will ask you some questions and do some tests to see if you qualify to take part in this research study. The study doctor will review the results of these questions, tests, and procedures. If you do not qualify, the study doctor will tell you why.

At this visit, we will:

- Ask about your medical history
- Give you some questionnaires to fill out about your general health and well-being
- Give you a physical exam, including measuring your height, weight, and vital signs
- Test your urine for drugs
- Draw a blood sample (about 4 tablespoons) for routine laboratory tests, if no recent tests performed at a Partners affiliated institution are available
- Test your urine for pregnancy, if you are a female able to become pregnant. Pregnant women cannot take part in this study.
- Do an ECG (electrocardiogram). This test checks the electrical activity of your heart. We will place several small, sticky pads on your chest, arms, and legs. Each pad has a wire attached. The wires connect to a machine that makes a recording of your heart rhythm. This painless test takes about 15 minutes.
- Please bring a copy of your insurance card to the screening visit for verification of health insurance coverage.

Urine Drug Screen

During this study, we will test your urine for certain drugs, including illegal drugs, such as cocaine and marijuana. If your urine shows you have taken any of these drugs, you can't be in this study. The results of the urine drug test will not become part of your medical record. These test results will, however, remain part of your study record.

Study Visit 2– EEG with ketamine

For safety reasons, you must have nothing to eat or drink for 8 hours before the study visit.

This visit will take about 3 hours to complete **and** will take place at the Carl Rosow Center for Clinical Research on White 5 at the MGH Main Campus.

If you are a female we will conduct another urine pregnancy test prior to the administration of ketamine.

Up to 256 EEG electrodes will be placed on your head using a special hat ("EEG cap"). This will not require us to remove any of your hair. A small amount of EEG paste will be applied to each electrode and directly to the skin of your scalp to improve contact with your skin.

We will place the following monitors on you:

- Heart monitor
- Blood pressure cuff
- Oxygen saturation monitor (plastic device that is put on your finger to measure the amount of oxygen in your blood)
- Skin conductance (how well your skin conducts electricity) will be measured with sensors placed on your fingers.
- Breathing volume (amount of air that is moved in and out of your lungs) will be measured using belts that are placed around your chest and abdomen (belly).
- Large cuff, similar to the blood pressure cuff, will be placed around your leg to produce a painful feeling (pain stimuli cuff).

You will have an IV catheter (small, flexible tube) placed in an arm vein. The IV catheter will be used to give you fluids or medications.

During the study, a board-certified anesthesiologist will be present whose sole responsibility will be to monitor your safety.

Ketamine will be given to you over the course of 5 minutes so that you will become drowsy and go under general anesthesia. This phase of the study will last for about 15-20 minutes. We will record your vital signs and brain waves (EEG) the entire time. We may administer a medication called glycopyrrolate if ketamine causes you to produce excessive saliva. We may also administer a medication called labetalol if ketamine causes high blood pressure.

During the baseline period, about 10-15 minutes before we start giving you ketamine and while you are getting it, we will present you with an auditory stimulus. During this time, you will listen to a series of "clicks" through a set of headphones placed in your ears. These clicks will be used to measure how your hearing functions while you are under anesthesia.

Next, you will hear a command to click a mouse. Your response to this command will help us determine whether or not you are under anesthesia. This overall pattern of clicks and verbal command sounds will be repeated many times. Before you are under anesthesia, we will practice this together until you become familiar and comfortable with the task. When you wake up and become aware of these sounds, you should continue performing the task.

During the baseline period and while you are waking up, we may inflate (blow up with air) the cuff on your leg to produce a painful feeling. This cuff is attached to a machine that controls the pressure of the air that will inflate the cuff. The pressure from this cuff is controlled and will be at a safe and tolerable range. The air pressure in the cuff will be increased for a period of time to cause slight discomfort. The pain should go away within several seconds after the cuff is deflated. Each individual experience of brief pain is called a pain stimulus. During the cuff calibration period, as well as throughout the study visit, you will be asked to rate your pain on a scale of 1 to

10. The following pain scale will be used to evaluate your pain: (1) 0-1 out of 10 as "tolerable"; (2) 2-3 out of 10 as "slight discomfort"; (3) 4-7 out of 10 as "moderate discomfort"; (4) 8-9 out of 10 as "painful"; and (5) 10 as "maximum pain."

While you are receiving the study drug, we may also begin an audio and video recording. The purpose of these recordings will be to relate your physical behavior to changes in your heart rate, blood pressure, breathing pattern, and oxygen intake during the transition to and from general anesthesia.

After you wake up, you will be asked to answer some questions to assess your thinking and wakefulness. These questions will be administered twice, 30 minutes apart, after which you will be given a dose of midazolam. Midazolam will be used to stop hallucinations that may be caused by ketamine during your recovery period. The dose of midazolam is similar to the dose doctors prescribe to relieve mild anxiety. You will be asked some final questions to evaluate your wakefulness and thinking for approximately 30 minutes.

After the study procedure is complete, you will recover and rest for 1-2 hours. We will remove the EEG electrodes at this time. During this time, we will monitor you to make sure that the effects of ketamine have worn off enough for you to go home.

You must have a responsible adult available to escort you home when you have completed the study. This responsible adult must be present regardless of the mode of transportation you choose, (for example, even if you take a cab or the bus). You cannot drive a motor vehicle, operate heavy machinery, drink alcohol, take any narcotic medications or medications that can cause drowsiness, or take part in any activity that requires alertness until 24 hours after you received the study drug. Additionally, we recommend that you consider taking the following day off, or at least refrain from driving, as some discomfort would not be unusual the following day. Time off work will not be considered an injury, and thus will not be covered by the study.

Use of the Audio or Video Recordings

Parts of the study will have educational and scientific value. Therefore, we may want to use the video for teaching purposes, presentations at medical/scientific meeting, or publications in a medical/scientific journal. In some cases, it may be necessary to show your face as part of the video presentation. You may request to review the video before you leave. If you are uncomfortable with the video recording, you may also ask that the video be never shown for teaching purposes, presentations at medical/scientific meeting, or publications in a medical/scientific journal.

I give the Investigators permission to use my video information <u>for the purposes research only and the video won't be shown to others</u>. _____ (Subject Initials)

-OR-

I give the Investigators permission to use my video information for the purposes of <u>research, teaching, medical/scientific presentations and/or publications.</u>
_____ (Subject Initials)

Stopping the Study Early

You may stop taking part in the study for any reason.

Also, the study doctor may take you out of the study without your permission. This may happen because:

- The study doctor thinks it is best for you to stop taking the study drug
- You can't make the required study visits
- We stop doing the study for other reasons

If this happens, the study doctor will explain why you need to stop taking part in the study.

If you should experience any concerning side effects following discharge (i.e. difficulty breathing, fevers, chest pain) please call 911 or proceed immediately to the nearest emergency room for evaluation. A study doctor will be available over the phone 24/7 to address any concerns. Please contact study doctors in the event of any post-discharge concerns (i.e. bruising at the IV site, tiredness, difficulty sleeping). MGH has an electronic system that lets your study doctors know if you are admitted to a Partners Hospital, or if you visit a Partners Hospital Emergency Department for any reason. This alert will let the study doctors know why you are there. We want to make sure the study doctors know about any possible problems or side effects you experience while you are taking part in the study.

What are the risks and possible discomforts from being in this research study?

Risks of Ketamine
Once enough ketamine has been given so that you are under general anesthesia, you may stop breathing on your own. This is an expected response to the ketamine. If this happens, the anesthesiologist will gently assist your breathing by placing a mask over your nose and mouth. This may be done for up to 15 minutes. Anesthesiologists are trained and routinely assist patient to breathe in the operating room. If this is done, you may notice a circular region of redness around your mouth and nose. There is also a slight chance that you may experience stomach insufflation and vomiting.

Ketamine may cause you to have one or more of the side effects listed below.

- high blood pressure
- increased heart rate
- irregular hear rate
- increased saliva
- increased mucus
- eye twitching
- hallucinations/clear dreams that may seem real
- confusion
- irritated feeling when waking up
- floating sensation (feeling "out-of-body") lasting from minutes to hours.
- breathing problems, coughing
- nausea, vomiting
- twitching, muscle jerks, and muscle tension
- increased thirst
- headaches
- metallic taste
- constipation
- blurry or double vision
- involuntary eye movements
- low mood or suicidal thoughts
- allergic reaction (skin rash)
- pain at site of injection
- increased intraocular pressure
- ulcerations and inflammation in the bladder

When giving any general anesthetic, there is always the possibility of very rare side effects or complications such as nerve damage, heart attack, brain damage, or even death. However, giving ketamine for sedation and maintenance of general anesthesia, at the doses you will receive in this study, is a standard practice in nearly every surgical center nationwide. Therefore, while the side effects and complications listed above are possible, life threatening side-effects are highly unlikely.

Any acute changes in heart rate or blood pressure observed during the study will be treated using standard anesthesiology practices.

Risks of Taking Glycopyrrolate

Glycopyrrolate is a drug that is used in the operating room every day. It is used to treat heart rate changes while a person is under general anesthesia. Glycopyrrolate may be given to you through the intravenous catheter to treat excessive salivation.
Common problems with glycopyrrolate (more than 1 out of 10) include dry mouth. Less common (between 1 and 10 out of 100) are abnormal heart rhythm (your heart not beating at an even pace), nausea, blurry vision and difficulty urinating.

Risks of Labetalol
Labetalol is a drug that is used to treat blood pressure changes while a person is under general anesthesia. Labetalol may be given to you through the intravenous catheter to decrease your blood pressure to a normal range. An anesthesiologist will monitor your blood pressure and heart rate and will give you labetalol to treat high blood pressure, if needed. Risks of labetalol include low blood pressure and low heart rate.

Risks of Intravenous (IV) Catheter
You may have a bruise (a black and blue mark) or pain where we place the IV. There is also a small risk of infection, lightheadedness, and fainting.

Risk of EEG Electrodes
There is a possibility that you may experience some redness or itching where the electrodes are placed.

Risks of Pain Stimuli Cuff
You may have a bruise (a black and blue mark) on your leg from the inflation of the cuff. In our experience, this is infrequent (occurs in less than 5 out of 100 people). A simple button press (controlled by the study team) can rapidly deflate the cuff, to make sure you are safe. The pain cuff will only be used when you are awake enough to talk to study team members. You can request that the cuff be deflated if it is too painful.

Risks of Allergic Reaction
As with any drug, an allergic reaction can occur. Allergic reactions can be mild or more serious, and can even result in death. Common symptoms of an allergic reaction are rash, itching, skin problems, swelling of the face and throat, or trouble breathing. If you think you are having an allergic reaction, tell the study doctor right away.

Risks to an Embryo or Fetus, or to a Breastfeeding Infant
The effect of ketamine on an embryo or fetus (developing baby still in the womb), or on a breastfeeding infant, is unknown and may be harmful. Because of these unknown risks, women cannot take part in this study if they are:

- Pregnant
- Trying to become pregnant

- Breastfeeding

If you are a menopausal woman and have not had a period for the past 12 months or more, you will not need to have a pregnancy test. Also, if you have had any well-documented method of surgical sterilization, you will not need to have a pregnancy test. The documented methods of surgical sterilization include having had a hysterectomy (removal of the uterus with or without the ovaries), bilateral oophorectomy (removal of both ovaries), a tubal ligation (having your tubes tied), or transvaginal occlusion (plugging the opening of the tubes with a coil.

What are the possible benefits from being in this research study?

You will not benefit from taking part in this study. What we learn in this study may help researchers develop improved anesthetics and anesthesia monitoring equipment in the future. It may also help researchers develop better pain management strategies. This may improve medical care for patients receiving anesthesia in the future.

Can I still get medical care within Partners if I don't take part in this research study, or if I stop taking part?

Yes. Your decision won't change the medical care you get within Partners now or in the future. There will be no penalty, and you won't lose any benefits you receive now or have a right to receive.

Taking part in this research study is up to you. You can decide not to take part. If you decide to take part now, you can change your mind and drop out later. We will tell you if we learn new information that could make you change your mind about taking part in this research study.

What should I do if I want to stop taking part in the study?

If you take part in this research study, and want to drop out, you should tell us. We will make sure that you stop the study safely. We will also talk to you about follow-up care, if needed.

Also, it is possible that we will have to ask you to drop out of the study before you finish it. If this happens, we will tell you why. We will also help arrange other care for you, if needed.

Will I be paid to take part in this research study?

We will pay you $500 if you complete both study visits.

If you complete the screening visit in good faith and are unable to continue for medical reasons, you will be compensated $50.

We will give you parking vouchers (coupons) to pay for your parking in the MGH garage during study visits.

What will I have to pay for if I take part in this research study?

Study funds will pay for certain study-related items and services. We may bill your health insurer for, among other things, routine items and services you would have received even if you did not take part in the research. You will be responsible for payment of any deductibles and co-payments required by your insurer for this routine care or other billed care. If you have any questions about costs to you that may result from taking part in the research, please speak with the study doctors and study staff. If necessary, we will arrange for you to speak with someone in Patient Financial Services about these costs."

What happens if I am injured as a result of taking part in this research study?

We will offer you the care needed to treat any injury that directly results from taking part in this research study. We reserve the right to bill your insurance company or other third parties, if appropriate, for the care you get for the injury. We will try to have these costs paid for, but you may be responsible for some of them. For example, if the care is billed to your insurer, you will be responsible for payment of any deductibles and co-payments required by your insurer.

Injuries sometimes happen in research even when no one is at fault. There are no plans to pay you or give you other compensation for an injury, should one occur. However, you are not giving up any of your legal rights by signing this form.

If you think you have been injured or have experienced a medical problem as a result of taking part in this research study, tell the person in charge of this study as soon as possible. The researcher's name and phone number are listed in the next section of this consent form.

If I have questions or concerns about this research study, whom can I call?

You can call us with your questions or concerns. Our telephone numbers are listed below. Ask questions as often as you want.

Oluwaseun Johnson-Akeju, MD, MMSC, is the person in charge of this research study. You can call him at 617-724-7200 Monday-Friday, 8am to 5pm. He can also be reached 24 hours a day, 7 days a week at (617) 726-2000, pager #13024.

If you have questions about the scheduling of appointments or study visits, call Jacob Gitlin at 617-643-2896 Monday-Friday, 8am to 5pm or by email at jgitlin1@partners.org.

If you want to speak with someone **not** directly involved in this research study, please contact the Partners Human Research Committee office. You can call them at 857-282-1900.

You can talk to them about:

- Your rights as a research subject
- Your concerns about the research
- A complaint about the research

Also, if you feel pressured to take part in this research study, or to continue with it, they want to know and can help.

If I take part in this research study, how will you protect my privacy?

Federal law requires Partners to protect the privacy of health information and related information that identifies you. We refer to this information as "identifiable information."

In this study, we may collect identifiable information about you from:

- Past, present, and future medical records
- Research procedures, including research office visits, tests, interviews, and questionnaires

Who may see, use, and share your identifiable information and why:

- Partners researchers and staff involved in this study
- The sponsor(s) of the study, and people or groups it hires to help perform this research or to audit the research
- Other researchers and medical centers that are part of this study

- The Partners ethics board or an ethics board outside Partners that oversees the research
- A group that oversees the data (study information) and safety of this study
- Non-research staff within Partners who need identifiable information to do their jobs, such as for treatment, payment (billing), or hospital operations (such as assessing the quality of care or research)
- People or groups that we hire to do certain work for us, such as data storage companies, accreditors, insurers, and lawyers
- Federal agencies (such as the U.S. Department of Health and Human Services (DHHS) and agencies within DHHS like the Food and Drug Administration, the National Institutes of Health, and the Office for Human Research Protections) state agencies, and foreign government bodies that oversee, evaluate, and audit research, which may include inspection of your records
- Public health and safety authorities, if we learn information that could mean harm to you or others (such as to make required reports about communicable diseases or about child or elder abuse)
- Other researchers within or outside Partners, for use in other research as allowed by law.

Certificate of Confidentiality

A federal Certificate of Confidentiality (Certificate) has been issued for this research to add special protection for information and specimens that may identify you. With a Certificate, unless you give permission (such as in this form) and except as described above, the researchers are not allowed to share your identifiable information or identifiable specimens, including for a court order or subpoena.

Certain information from the research will be put into your medical record and will not be covered by the Certificate. This includes records of medical tests or procedures done at the hospitals and clinics, and information that treating health care providers may need to care for you. Please ask your study doctor if you have any questions about what information will be included in your medical record. Other researchers receiving your identifiable information or specimens are expected to comply with the privacy protections of the Certificate. The Certificate does not stop you from voluntarily releasing information about yourself or your participation in this study.

Even with these measures to protect your privacy, once your identifiable information is shared outside Partners, we cannot control all the ways that others use or share it and cannot promise that it will remain completely private.

Because research is an ongoing process, we cannot give you an exact date when we will either destroy or stop using or sharing your identifiable information. Your permission to use and share your information does not expire.

The results of this research may be published in a medical book or journal, or used to teach others. However, your name or other identifiable information **will not** be used for these purposes without your specific permission.

Your Privacy Rights

You have the right **not** to sign this form that allows us to use and share your identifiable information for research; however, if you don't sign it, you can't take part in this research study.

You have the right to withdraw your permission for us to use or share your identifiable information for this research study. If you want to withdraw your permission, you must notify the person in charge of this research study in writing. Once permission is withdrawn, you cannot continue to take part in the study.

If you withdraw your permission, we will not be able to take back information that has already been used or shared with others, and such information may continue to be used for certain purposes, such as to comply with law or maintain the reliability of the study.

You have the right to see and get a copy of your identifiable information that is used or shared for treatment or for payment. To ask for this information, please contact the person in charge of this research study. You may only get such information after the research is finished.

Informed Consent and Authorization

Statement of Person Giving Informed Consent and Authorization

- I have read this consent form.
- This research study has been explained to me, including risks and possible benefits (if any), other possible treatments or procedures, and other important things about the study.
- I have had the opportunity to ask questions.
- I understand the information given to me.

Signature of Subject:

I give my consent to take part in this research study and agree to allow my identifiable information to be used and shared as described above.

Subject	Date	Time (optional)

Signature of Study Doctor or Person Obtaining Consent:

Statement of Study Doctor or Person Obtaining Consent

- I have explained the research to the study subject.
- I have answered all questions about this research study to the best of my ability.

Study Doctor or Person Obtaining Consent	Date	Time (optional)

Consent Form Version Date: 10/17/2018