Title: Assessing the Cortical Response to Noxious and Auditory Stimuli Using Near Infrared Spectroscopy in Subjects under General Anesthesia

NCT: NCT02703090

Date: September 25, 2017

Please check one of the following:

_____ You are an adult participant in this study.

_____ You are the parent or guardian granting permission for a child in this study.

If the participant is a child the use of "you" refers to "your child"

This consent form gives you important information about a research study. A research study helps scientists and doctors learn new information to improve medical practice and patient care.

Participation in this research study is voluntary. You are free to say yes or no and your decision will not impact the care you receive at Boston Children's Hospital. You can withdraw from the study at any time. A description of the study and its risks, potential benefits and other important information are in this consent form. Please read this consent form carefully and take your time making a decision. The form may contain words that you do not understand. Please ask questions about anything you do not understand. We encourage you to talk to others (for example, your friends, family, or other doctors) before you decide to participate in this research study.

How are individuals selected for this research study?

You are being asked to participate in this research study because you are scheduled to undergo a routine cardiac catheterization for treatment of your irregular heart rhythm. Your name was obtained from the list of patients scheduled to undergo a cardiac catheterization for treatment of an irregular heart rhythm.

Why is this research study being conducted?

In this research study we want to learn more about how near infrared spectroscopy can be used to measure activation of the brain in patients under general anesthesia.

Spectroscopy is a technique that uses light to measure the amount of a colored compound dissolved in a solution.

Near-infrared light (light not visible to the human eye) has the ability to pass through human tissues and is thus used in spectroscopy instruments for measurements on patients.

A *colored compound* that is measured with near-infrared spectroscopy is hemoglobin, a molecule found in the blood, which carries oxygen to all tissues of the body.

When an area of the brain is activated, there is an increase in blood flow to the activated area which results in an increase in the amount of hemoglobin carrying oxygen to the activated brain region. By measuring activation of the brain in this way, we hope to develop our near-infrared instrument into a reliable way of determining whether a patient undergoing surgery with general anesthesia is not experiencing any pain and is truly asleep and unaware of their surroundings.

As part of measuring brain activation, it is important to determine whether an FDA-approved pain medication called remifentanil changes the pattern of brain activation in response to the stimulation associated with the planned procedure. Remifentanil is a very short-acting medicine commonly used during surgical procedures to reduce pain.

The machine we will be using has been approved by the U.S. Food and Drug Administration (FDA) for research purposes only. Information from this research will help determine whether the monitor should be approved by the FDA in the future for routine use on patients.

Who is conducting this research study, and where is it being conducted?

The Principal Investigator is Barry D. Kussman, MBBCh, who is a senior anesthesiology attending at Boston Children's Hospital. This is a single site study only being conducted at Boston Children's Hospital. The research is being sponsored by the Department of Anesthesiology, Perioperative and Pain Medicine, Boston Children's Hospital.

Your health care provider may be a research investigator for this research and as an investigator, is interested in both your clinical welfare and in the conduct of this study. Before entering this study or at any time during the research, you may ask for a second opinion about your care from another health care provider who is in no way associated with this project. You are not under any obligation to participate in any research project offered by your health care provider. If you choose not to participate or not to allow your child to participate, your care at Boston Children's Hospital and/or with your health care provider will not be affected in any way at all.

How many people will participate in this research study?

Approximately 54 people will take part in this study at Boston Children's Hospital.

What do I have to do if I am in this research study?

At your **pre-catheterization work-up**, we will explain all the steps of the study and ask you to complete a Pre-Operative Questionnaire asking questions such as hair color, hair thickness, whether you are right- or left-

handed, if you have any hearing problems, and your contact information. The questionnaire may be completed at home and given to the study staff on the day of and prior to the procedure. Explanation of the study with completion of the questionnaire will take approximately 30 minutes.

On the **day of the procedure** we will again go over the steps in the study and what you need to know and do. General anesthesia is a standard part of the catheterization procedure, and the study will be done during the same period of anesthesia. If you choose to participate in this study, you will still receive all of the medicines that you would normally receive for your procedure. You will have the option of withdrawing from the study at any time before anesthesia is begun. Because no one knows which dose of remifentanil is best, you will be "randomized" into one of three study groups. Randomization means that you are put into a group by chance. It is like flipping a coin. You will have a one in three chance of being placed in any group. Neither you nor the research investigator can choose what group you will be in. One group will receive a placebo (normal saline/salt water), one group will receive a lower dose of remifentanil (0.25 mcg/kg/minute), and the other group will receive a higher dose of remifentanil (0.5 mcg/kg/minute). The doses are the same as those routinely used during surgery. While the effectiveness of remifentanil in blocking pain signals measured with near infrared spectroscopy during the type of procedure that you are having has not been studied, the medication itself is approved for use as a pain medication and is not experimental in any way. You should know that the placebo is an infusion of normal saline that does not contain any medicine and we do not expect it will be harmful or do anything to your health. We use a placebo so we do not know whether you are receiving the drug or not.

Depending on which group you were randomized (automatically allocated) to, the normal saline or remifentanil (two dosage groups) will be prepared by and obtained from the pharmacy. Before anesthesia is administered, study personnel will position the near infrared light probes (optodes) on your head by placing a cap on your head. The probe holder (cap) is not constricting, and any discomfort is minimized by surrounding the probes with foam tape and using soft cloth straps against the head, face and chin. After initial positioning, the probe may need to be shifted slightly until an adequate signal is obtained from all the probes. The probes are 1-3mm in diameter, allowing them to be easily wiggled through the hair to make appropriate contact with the scalp. In some cases, hair will be parted in order to achieve better contact, but no shaving of hair will be necessary.

You will then be asked to perform a brief finger tapping exercise, tapping the fingers of the left hand against the thumb for 5 seconds, with 15 seconds between, for 5 cycles. This exercise ensures proper positioning of the probe holder and probes on the head. The probe holder may need to be shifted to obtain a better signal, and the tapping exercise may need to be repeated. If no signal is obtained after several tries, you will not be able to participate in the study. In a similar manner, we will lightly stroke the top of your hand with a piece of Velcro to ensure adequate signals are being detected by the probes.

Afterwards, we will place headphones on your head and an audio recording will be played prior to anesthesia. This data will be used as baseline consciousness data and to familiarize you with the study procedures. The audio will request that you imagine squeezing a tennis ball in a clasping motion, without actually performing

the action, with the same hand used for the finger tapping exercise and stroking. During this we expect to see brain activity in the movement (motor) area if you are consciously aware.

The above process will take about 20 minutes, and has been approved by the cardiologist performing the catheterization procedure.

After anesthesia is begun (i.e. you are asleep for the catheterization procedure), we will play the audio recording every half hour during your anesthesia. Also, once you are asleep, we will put one additional sticker on your forehead. This sticker is called a BIS (Bispectral Index) Monitor. It is a sticker that doctors sometimes use during procedures to make sure the patient is deeply asleep during their procedure. The BIS Monitor will be removed from your forehead at the end of your procedure just before or just after you wake up from anesthesia.

Additionally, soon after are asleep, your anesthesiologist will start the infusion (administration) of the normal saline or remifentanil. This medicine will be given to you through an intravenous (IV) catheter that will already be in place as a routine part of your procedure. An IV catheter is a small, flexible tube made of plastic that is routinely inserted into a vein by one of the doctors taking care of you during your procedure. The catheter is used to give medicine and fluid to you during the procedure. The remifentanil infusion will end once your cardiologist is finished with your procedure and before you wake up from anesthesia. Apart from the remifentanil, the anesthesia care will be the same as if you were not participating in this study. The headphones and probe cap will be removed from your head before you wake up from anesthesia. The duration of anesthesia will not be prolonged by the study.

Before you are discharged from the hospital, you will be asked to fill out a Post-Operative Questionnaire. The questions on this questionnaire are routinely used by anesthesiologists to determine if a patient was awake or aware during general anesthesia. Questions will ask about any memories during the surgery, the last thing remembered before going off to sleep, the first thing remembered upon waking up, and whether you had any dreams during the procedure. The Post-Operative Questionnaire will take approximately 10 minutes. If we are unable to complete this questionnaire before you leave the hospital, we may call you and ask you to answer the questions over the telephone.

You will be telephoned about a month following the procedure and asked the same questions as on the postoperative questionnaire (because in the immediate postoperative period the residual effects of anesthetics may impair memory function). The Post-Operative Questionnaire will take approximately 10 minutes.

You will be in this research study for about 5 to 6 hours total depending on the length of your procedure. This includes the time required for the research study on the day of your pre-operative visit, the time required on the day of your procedure, and the follow-up phone call a month after your procedure.

Additionally, we will collect some information from your medical record about your procedure and hospital stay.

Since the expectations of patients and doctors can influence the results of a study, neither you nor the research investigators analyzing the results of this study will know which drug you got until the study is over. But, if there is a medical emergency, the research investigator will be able to get this information i.e. whether you received remifentanil and at what dose.

.What are the risks of this research study? What could go wrong?

There are no known risks associated with the use of near infrared spectroscopy (NIRS). Near infrared spectroscopy is used routinely in many hospitals, including Boston Children's Hospital, in the operating room during cardiac surgery, in the cardiac intensive care unit, and in medical-surgical intensive care units. The NIRS system we will use in this study has been approved by the FDA for research purposes, and is a relatively new way to measure activity in the brain. No harmful effects have been reported so far, but it is possible that you may experience side effects that we don't know about yet. The near infrared light used is much less intense than the near infrared light from sunlight you would feel during an outdoor walk on a sunny day. There is no x-ray radiation from the NIRS system.

The cap holding the probes is not constricting and is easily removed. It is lined with foam and soft Velcro strips to minimize any discomfort. There are no known complications with this cap.

It is possible that when the BIS monitor sticker is removed from your forehead at the end of your procedure, your skin may be a little red. This redness should go away on its own while you are in the recovery room.

The risks related to receiving remifentanil as part of this study are the possibility of increased nausea and vomiting and sleepiness after the procedure. The catheterization procedure itself, however, is associated with nausea and vomiting, and additional nausea and vomiting from the remifentanil is unlikely to occur as this medicine only lasts in the body for a very short time. Also, as part of your routine care, your anesthesiologist will give you a medicine to help with nausea and vomiting associated with your procedure and anesthesia. Increased sleepiness after the procedure is also very unlikely because remifentanil only acts for a few minutes after the drug is stopped.

Every effort will be made to protect and assure your privacy. Only the study investigators, doctors, and nurses caring for you during the cardiac catheterization will know that you are enrolled in the study. You will not be seen in any research areas that may stigmatize you.

Some procedures or treatments used in this research may present risks that are not well-known or understood. Therefore, there may be unforeseeable risks associated with participating in this research.

What are the benefits of this research?

Being in this research will not help you right now. Eventually we hope to develop the technology into a reliable monitor for determining whether a patient receiving general anesthesia is not experiencing any pain, and is truly asleep and unaware of their surroundings.

Are there costs associated with this research? Will I receive any payments?

You will be given a $30.00 Amazon Gift Card for completing this study. You will receive the card either in the recovery area after your procedure or the ward before you are discharged from hospital.

We will offer you the care needed to treat any injury that directly results from taking part in this research. 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, tell the person in charge of the research as soon as possible. The researcher's name and phone number are listed in this consent form.

Are there other things I should know about?

The only difference in your anesthesia if you choose to be in the study will be the administration of normal saline or remifentanil. All other drugs and techniques of the anesthesia will be the same as standard (usual) care. Intravenous opioids (pain medicines) are typically not given after the beginning of general anesthesia so that there is no different or reduced pain control than normal (i.e. if you were not in the study).

If we find out about new information from this research or other research that may affect your health, safety or willingness to stay in this research we will let you know as soon as possible.

From time to time, Boston Children's Hospital licenses some of its research discoveries to for profit companies for further research and/or commercial development. Boston Children's Hospital and the Massachusetts General Hospital own patents related to this research. Sometimes the inventor of the research receives equity (partial ownership of the company) in such licensing arrangements. It is also possible that a research investigator conducting a study may be paid for providing consulting services to a company that funds the research. In this research, David Boas, PhD has a financial interest in the technology that is used in this research. David Boas is an inventor on a technology licensed to TechEn, a company whose medical pursuits focus on noninvasive optical brain monitoring. Dr. Boas's interests were reviewed and are managed by Massachusetts General Hospital and Partners HealthCare in accordance with their conflict of interest policies.

In the future it is possible that this technology will be sold commercially, and that the results of this trial will be important in securing government approval or contracting with a business to manufacture or develop the technology. If this were to occur, Boston Children's Hospital and the investigators might receive financial benefits in the form of royalties or other compensation. As in all research studies, the Hospital has taken steps designed to ensure that this potential for financial gain does not endanger research subjects, or undercut the validity and integrity of the information learned by this research."

Why would I be taken off the study early?

The research investigator may take you out of this study at any time. This would happen if:

- The research is stopped.
- Your procedure is cancelled.
- The research investigators are unable to get good light signals, even after shifting the cap.
- The equipment is not working properly.
- The doctors taking care of you feel it is in your best interest to be taken out of this research. An example would be low blood pressure during evaluation of the irregular heart rhythm.
- The cardiologist is not able to or decides not to ablate the cause of the irregular heart rhythm.

If this happens, the research investigator will tell you. If the doctors feel it is in your best interest to be taken out of this research, the data from your participation may or may not be used depending on when this happens during the procedure.

Other information that may help you:

Boston Children's Hospital has developed a web-based, interactive educational program for parents called "A Parent's Guide to Medical Research." To find out more about research at Children's, please visit the program at www.researchchildren.org.

Boston Children's Hospital is interested in hearing your comments, answering your questions, and responding to any concerns regarding clinical research. If you have questions or concerns, you may email IRB@childrens.harvard.edu or call (617) 355-7052 between the hours of 8:30 and 5:00, Monday through Friday.

Who may see, use or share your health information?

A copy of this consent form will be placed in your medical record.

The results of the tests performed for research purposes will not be placed in your medical record. Because of this, it is unlikely that others within the hospital, an insurance company, or employer would ever learn of such results.

All records associated with your participation in this study will be confidential. However, because the use of this device is regulated by the Food and Drug Administration (FDA), agents of the FDA may have access to these records during the course of their duties.

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.

Contact for Future Studies: Your participation in any research is completely voluntary and you should feel no pressure to participate if you are contacted about another research study.

Please check and initial one of the options below regarding future contact about other research done by us or other researchers we are working with (collaborators).

_____ ☐ Yes, I may be contacted about participating in other research projects studying NIRS and brain activation. I give permission for my contact information (name and mailing address and/or phone number) to be given to other researchers working with the study investigator at Boston Children's Hospital.

_____ ☐ No, I do not want to be contacted about other research projects. **Do not** give my contact information to the staff of any other research studies.

What should you know about HIPAA and confidentiality?

Your health information is protected by a law called the Health Information Portability and Accountability act (HIPAA). In general, anyone who is involved in this research, including those funding and regulating the study, may see the data, including information about you. For example, the following people might see information about you:

- Research staff at Boston Children's Hospital involved in this study;
- Medical staff at Boston Children's Hospital directly involved in your care that is related to the research or arises from it;
- Other researchers and centers that are a part of this study, including people who oversee research at that hospital;

- People at Boston Children's Hospital who oversee, advise, and evaluate research and care. This includes the ethics board and quality improvement program;
- People from agencies and organizations that provide accreditation and oversight of research;
- People that oversee the study information, such as data safety monitoring boards, clinical research organizations, data coordinating centers, and others;
- Sponsors or others who fund the research, including the government or private sponsors.
- Companies that manufacture drugs or devices used in this research;
- Federal and state agencies that oversee or review research information, such as the Food and Drug Administration, the Department of Health and Human Services, the National Institutes of Health, and public health and safety authorities;
- People or groups that are hired to provide services related to this research or research at Boston Children's Hospital, including services providers, such as laboratories and others;
- And/or your health insurer, for portions of the research and related care that are considered billable.

If some law or court requires us to share the information, we would have to follow that law or final ruling.

Some people or groups who get your health information might not have to follow the same privacy rules. Once your information is shared outside of Boston Children's Hospital, we cannot promise that it will remain private. If you decide to share private information with anyone not involved in the study, the federal law designed to protect privacy may no longer apply to this information. Other laws may or may not protect sharing of private health information. If you have a question about this, you may contact the Boston Children's Hospital Privacy Officer at (857) 218-4680, which is set up to help you understand privacy and confidentiality.

Because research is ongoing, we cannot give you an exact time when we will destroy this information. Researchers continue to use data for many years, so it is not possible to know when they will be done.

We will also create a code for the research information we collect about you so identifying information will not remain with the data and will be kept separately. The results of this research may be published in a medical book or journal or be used for teaching purposes. However, your name or identifying information will not be used without your specific permission.

Your privacy rights:

If you want to participate in this research study, you must sign this form. If you do not sign this form, it will not affect your care at Boston Children's Hospital now or in the future and there will be no penalty or loss of benefits. You can withdraw from the study and end your permission for Boston Children's Hospital to use or share the protected information that was collected as part of the research; however you cannot get back information that was already shared with others. Once you remove your permission, no more private health

information will be collected. If you wish to withdraw your health information, please contact the research team.

You may have the right to find out if information collected for this study was shared with others for research, treatment or payment. You may not be allowed to review the information, including information recorded in your medical record, until after the study is completed. When the study is over, you will have the right to access the information again. To request the information, please contact the Hospital's Privacy Officer at (857) 218-4680.

Contact Information:

I understand that I may use the following contact information to reach the appropriate person/office to address any questions or concerns I may have about this study. I know:

I can call…	At	If I have questions or concerns about
Investigator: **Barry Kussman, MBBCh**	Phone: **617-355-6225** Pager: 617-355-7243 **#2373**	▪ General questions about the research ▪ Research-related injuries or emergencies ▪ Any research-related concerns or complaints
Co-Investigator: David Borsook, MBBCh, PhD	Phone: **617-855-2691**	▪ General questions about the study ▪ Research-related injuries or emergencies ▪ Any research-related concerns or complaints
Institutional Review Board	Phone: **617-355-7052**	▪ Rights of a research participant ▪ Use of protected health information. ▪ Compensation in event of research-related injury ▪ Any research-related concerns or complaints. ▪ If investigator/research contact cannot be reached. ▪ If I want to speak with someone other than the Investigator, Research Contact or research staff.

Documentation of Informed Consent and Authorization

- I have read this consent form and was given enough time to consider the decision to participate in this research.
- This research has been satisfactorily explained to me, including possible risks and benefits.
- All my questions were satisfactorily answered.
- I understand that participation in this research is voluntary and that I can withdraw at any time.
- I am signing this consent form prior to participation in any research activities.

- I give permission for participation in this research and for the use of associated protected health information as described above (HIPAA).

Parent/Legal Guardian Permission (if applicable)

If the child to be involved in this research is a foster child or a ward of the state please notify the researcher or their staff who is obtaining your consent.

■ _____ _____ _____

Date (MM/DD/YEAR) Signature of **Parent #1** or **Legal Guardian** Relationship to child

■ _____ _____ _____

Date (MM/DD/YEAR) Signature of **Parent #2** Relationship to child

☐ CHECK if 2nd parent signature **not** obtained above. The PI must document in research records all attempts made to contact the second parent, as well as the reason why the 2nd parent signature was not obtained.

■ If child/adolescent's assent is **not** documented, please indicate reason below (check one):

☐ Assent is documented on a separate IRB-approved assent form
☐ Child is too young
☐ Other reason (e.g. sedated), please specify: _____

Adult Participant (if applicable)

■ _____ _____

Date (MM/DD/YEAR) Signature of **Adult Participant (***18+ years)*

Research Investigator /or Associate's Statement & Signature

- I have fully explained the research escribed above, including the possible risks and benefits, to all involved parties (participant /parents/legal guardian as applicable).
- I have answered and will answer all questions to the best of my ability.
- I will inform all involved parties of any changes (if applicable) to the research procedures or the risks and benefits during or after the course of the research.

- I have provided a copy of the consent form signed by the participant / parent / guardian and a copy of the hospital's privacy notification (if requested).

■ _____ _____

Date (MM/DD/YEAR) Signature of **Research Investigator or Associate**

Witness Statement & Signature

A witness must be present for the entire consent process in the following situations (please check the appropriate box)

☐ The individual cannot read and this consent document was read to the participant or legal representative, **or**

☐ The individual has certain communication impairments that limit the participant's ability to clearly express consent **or**

☐ Situations where the IRB requests a witness be present: please specify _____

I confirm that the information in this consent form was accurately explained to the participant, parent or legally authorized representative, the individual appeared to understand the information and had the opportunity to ask questions, and that informed consent was given freely.

☐ _____ _____

Date (MM/DD/YEAR) Signature of **Witness**