UNIVERSITY OF PENNSYLVANIA
RESEARCH SUBJECT
INFORMED CONSENT & HIPAA AUTHORIZATION FORM

Protocol Title:	**Two-Part Study to Evaluate the Safety and Efficacy of Image Guided Surgery using Near-Infrared dyes for Intramolecular Imaging of Nervous System Tumors Compared to Standard of Care, (TumorGlow™)**
Principal Investigator:	John Lee, MD Department of Neurosurgery 235 S 8th Street Philadelphia, PA 19106 #215-829-6700
Emergency Contact:	Neurosurgery Resident On-call 215-829-3000

Why am I being asked to volunteer?

You are being invited to participate in a research study because you are having brain, spine, or peripheral nerve (nervous system) tumor surgery. Your participation is voluntary which means you can choose whether or not you want to participate. If you choose not to participate, there will be no loss of benefits to which you are otherwise entitled. Before you can make your decision, you will need to know what the study is about, the possible risks and benefits of being in this study, and what you will have to do in this study. The research team is going to talk to you about the research study, and they will give you this consent form to read. You may also decide to discuss it with your family, friends, or family doctor. You may find some of the medical language difficult to understand. Please ask the study doctor and/or the research team about this form. If you decide to participate, you will be asked to sign this form.

What is the purpose of this research study?

The purpose of this study is to determine if an intravenous injection of indocyanine green detected by using an imaging system can be a useful tool to identify tumor from normal tissues. In addition, this study will assess whether a dose of indocyanine green larger than is currently approved is safe to use. Indocyanine green has been used in a clinical setting for over sixty (60) years for mapping the blood vessels of the eye, liver blood flow tests, and heart function tests. Because the drug has not been approved for use in the manner in which we are proposing, this research is considered experimental.

How long will I be in the study?

Your participation in the study will last from your screening visit until the end of your surgery (approximately 2-4 weeks). However, at the conclusion of your active participation, we will collect your health information for a period of up to five (5) years. You will not have to return to the hospital for this portion of the study. The Principal Investigator and research team will review your medical records for the period of up to five (5) years to obtain information about your medical condition. The study as a whole is expected to last about five years. We expect to enroll a total of 500 patients from The University of Pennsylvania Heath System.

What am I being asked to do?

Administration of NIR drug:

Permitting infusion time within 72 hours of operation is believed by the Investigator to be adequate for tissue glow/surgical visualization. Data analysis will determine optimal timing of indocyanine green infusion. For your operation you will go to either the Hospital of University of Pennsylvania (HUP); Perelman Center for Advanced Medicine Clinical & Translational Research Center, 3400 Civic Center Blvd., Philadelphia PA, 19104 or the Abramson Cancer Center at Pennsylvania Hospital (PAH), 230 W. Washington Square, Philadelphia PA, 19106 or the Abramson Cancer Center at Penn Presbyterian Medical Center (PPMC), 1st floor CUPP Building, 51 N 39th St, Philadelphia, PA 19104 to receive a single dose of indocyanine green. This indocyanine green dose is within range of other research studies (including studies with the liver). The nurse will place a peripheral IV (intravenous catheter) for the indocyanine green infusion. The injection of the indocyanine green is expected to take about 40 to 60 minutes. You will be monitored before, during and after the injection for signs of anaphylaxis (see below).

Alternately, based on neurosurgeon plan, patients may receive a 25 mg bolus of ICG at the time of induction administered intravenously by the anesthesiologist.

Standard of care dyes such as Gleolan, is the first *and only* FDA approved optical imaging agent for use in Fluorescence-Guided Surgery. Gleolan™ [aminolevulinic acid hydrochloride (ALA HCl)] is an optical imaging agent indicated in patients with glioma (suspected World Health Organization Grades III or IV on preoperative imaging) as an adjunct for the visualization of malignant tissue during surgery. It is orally administered 2-4hours prior to anesthesia.

In this current study, we may intend to compare SOC dyes with indocyanine green to find out which dye is more accurate and precise. This may lead to patients receiving more than one (1) drug prior surgery and visualizing the tumor with different cameras during surgery. This may result in added time to your surgical procedure.

There are no additional risks of administering both dyes together. In this study, there is no anticipated risk by extending the surgical procedure and imaging both dyes together.

When you return for your operation, during your surgery for a period of five (5) to ten (10) minutes, before resection, during resection, and after resection, the surgeon will take video images of your tumor with a specialized imaging system.

Once the tumor is removed, if the surgeon sees any remaining glowing tissue, he/she will resect the area if it is safe to do so. There may be instances that the area cannot be removed or biopsied without significantly changing the operation, specifically for safety concerns. In that event, the nodule will be left in place. Once the tumor is removed, a small section of the tissue will be sent to pathology for standard processing. The imaging procedure is expected to add another five (5) to ten (10) minutes to the time your operation would normally last. Indocyanine green is typically eliminated by the liver. Weight, height, age, overall health, etc. all factor into how fast your body eliminates the indocyanine green.

The injection and recording of the indocyanine green activity with the imaging machines, along with removal of tissue that will be glowing, are the only experimental procedures to be performed in this study.

For a period of up to five (5) years after your enrollment in this clinical study, the Principal Investigator and research team will review your medical records to obtain information about your medical condition.

What are the possible risks or discomforts?

Indocyanine Green Risks/Discomfort:

Indocyanine green is known to have a rare but serious side effect known as anaphylaxis, a form of allergic reaction, especially in patients with iodide allergies. For example, iodides are found in shellfish. If you have an allergy to iodides, you will not be allowed to participate in this study.

Anaphylaxis
Anaphylaxis is an allergic reaction to a substance, which can cause inflammation (swelling) of the skin, shortness of breath, dizziness, increased heart rate, rash, and possibly death. As you will be given indocyanine green in a procedure room with trained nurses, you will be closely monitored for anaphylaxis via steady collection of your heart rate, blood pressure, oxygen levels and skin color. In the event of an anaphylactic reaction, injection will be stopped and drugs will be used to control the reaction.

Hypertension
Infusion of indocyanine green may need to be stopped if you have symptoms of hypertension (high blood pressure) at any level or, do not have symptoms but your diastolic blood pressure is elevated >100 or systolic >200. The doctor is notified when the BP elevations reach levels of concern.

Mild Arm Discomfort/Pain
Subjects may experience arm/shoulder pain or discomfort at the site of infusion. If this occurs, the nursing staff will apply a hot pack or compress at the area of pain. Infusion of indocyanine green may be stopped if the pain is too great or the pain has not stopped.

General Disorders
Other symptoms, such as fatigue (getting tired), headache, fever-like symptoms, itching, etc., may occur. The doctor will be consulted for treatment and infusion decisions.

Administration Site Conditions
Subjects may experience tenderness or muscle spasms during the infusion. If this occurs, the nursing staff will evaluate as necessary and provide a hot pack/compress to the IV site. If you experience extravasion of the drug, the infusion may be changed to the other arm or discontinued.

Gastrointestinal Disorders
Subjects may become nauseous during the infusion. If this occurs, the infusion is discontinued.

Impact of Indocyanine Green on Pulse Oximetry Readings
Subjects may experience a slight decrease of pulse oximetry readings (blood oxygen level). To date, no treatment has been necessary, as pulse oximetry readings return to normal following completion of infusion.

Video Imaging
The video images that we will take may result in your surgeon changing your operation. Your surgeon will not change the magnitude of the operation to do anything that was not described to you when you agreed to undergo the surgery. If the surgeon images your tumor with multiple cameras and/or NIR dyes, your surgical procedure may be extended. However, your surgeon will keep the imaging to 15 minutes.

However, because the video images are being taken as part of a research study, they do come with some risks:

- There is a chance that an area that does not have any tumor will glow in the video images. If that happens, your surgeon may remove healthy tissue that did not need to be removed and that would not have been removed in a standard surgery.
- There is a chance that while removing additional tissue that glows in the video images you could be put at an increased risk of having a surgical complication.

Finally, there is a chance that the imaging technique may falsely reassure the surgeon that all of the tumor has been taken out, so not as much tissue will be removed. In other words, not all of the tumor could be taken out.

Your surgeon will do everything possible to minimize these risks. If your surgeon thinks that removing the additional tissue is too risky, they will not remove the additional tissue.

<u>Risks of Gleolan (aminolevulinic acid hydrochloride (ALA HCl) (5-ALA):</u>

- Adverse reactions occurring in >1% of patients in the week following surgery were pyrexia, hypotension, nausea, and vomiting.
- Adverse reactions occurring in < 1% of patients in the first 6 weeks after surgery were: chills, photosensitivity reaction, solar dermatitis, hypotension, abnormal liver function test, and diarrhea.
- Neurologic events related to the surgical procedure occurred in 29% of patients and included: aphasia, hemiparesis, hemianopia, headache, seizure, hemiplegia, monoparesis, hypoesthesia, and brain edema.
- Elevated liver enzymes occurred in clinical studies.

Surgical Complication
A surgical complication includes, but is not limited to:

- Impaired brain function, bleeding, infection, pain, injury to a major organ, nerve damage, blood clot in the arms/legs/other region of the body, and death.

Risk of Anesthesia
There is a chance that being under anesthesia for the additional fifteen (15) to twenty (20) minutes, you could be put at an increased risk of having of a common side effect associated with anesthesia. These common side effects include, but are not limited to:

- Nausea and vomiting after surgery, sore throat and hoarseness, shivering/chills, confusion, increased blood pressure and muscle aches.

Reproductive Risks

Indocyanine green has no known side effects to a pregnant or nursing mother. Indocyanine green does not have any known fetal toxicity. Nevertheless, we are NOT enrolling pregnant or nursing mothers in the study. If you are currently pregnant, it is important that you inform the investigator because you will not be able participate in the study. If you are able to become pregnant, you will be given a blood or urine pregnancy test before entry into the study. If the test is positive, you will not be able to participate in this study.

It is possible that there are additional risks involved with the use of indocyanine green and/or gleolan that are unknown at this time.

What if new information becomes available about the study?
During the course of this study, we may find more information that could be important to you. This includes information that, once learned, might cause you to change your mind about being in the study. We will notify you as soon as possible if such information becomes available.

What are the possible benefits of the study?
Most likely, no direct medical benefit will come to the subjects of this research project. The proposed study may generate important data regarding your tumor and prognoses. We do not know whether these video images truly identify tumor however, there is a chance that because of the video images your surgeon will remove additional tumor that they would not have removed during a standard operation. Pathology will occur on any “glowing” tissue that is removed and an official report will be generated.

In addition, your participation may make it possible for future patients diagnosed with tumors to benefit from the information that we collect during your participation.

What other choices do I have if I do not participate?

Your other option is to not participate in this study. Your decision to participate will in no way affect your care. Alternative treatment/surgery to being in this study can be discussed with your personal physician.

Will I be paid for being in this study?

You will not be paid for your participation in this study**.**

Will I have to pay for anything?

You will not have to pay for the study medications or costs directly relating to the experimental procedure.

You and/or your health insurance may be billed for the costs of medical care during this study if these expenses would have happened even if you were not in the study.

What happens if I am injured from being in the study?

We will offer you the care needed to treat injuries directly resulting from taking part in this research. We may bill your insurance company or other third parties, if appropriate, for the costs of the care you get for the injury, but you may also be responsible for some of them.

There are no plans for the University of Pennsylvania to pay you or give you other compensation for the injury. You do not give up your legal rights by signing this form.

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

When is the Study over? Can I leave the Study before it ends?

This study is expected to end after all participants have completed all visits, and all information has been collected. This study may also be stopped at any time by your physician, the study Sponsor, or the Food and Drug Administration (FDA) without your consent because:

- The Primary Investigator feels it is necessary for your health or safety. Such an action would not require your consent, but you will be informed if such a decision is made and the reason for this decision.
- You have not followed study instructions.
- The Sponsor, the study Principal Investigator, or the Food and Drug Administration (FDA) has decided to stop the study.

If you decide to participate, you are free to leave the study at any time. Withdrawal will not interfere with your future care.

Who can see or use my information? How will my personal information be protected?

We will do our best to make sure that the personal information obtained during the course of this research study will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. If this study is being overseen by the Food and Drug Administration (FDA), they may review your research records. Your privacy and the protection of your health information are important to us. This section of the consent will cover:

- What personal health information about you will be collected in this study?
- Who will use your information within the institution and why?
- Who may disclose your information and to whom?
- Your rights to access research information about you.
- Your right to withdraw your authorization (approval) for any future use of your personal health information.

What Information about me may be collected, used or shared with others?

The following personal health information will be collected, used for research and may be disclosed or released during your involvement with this research study.

- Name
- Address
- Telephone Number
- Elements of dates
- Medical Record Number
- Results of information used in the management or diagnosis of your tumor, including history, physical and neurologic examination, laboratory studies, and/or imaging studies
- Personal Medical History, current and past medications or therapies
- Previous advanced imaging that may have been collected outside of the University of Pennsylvania Hospital

Why is my information being used?

Your information is used by the research team to contact you during the study. Your information and results of tests and procedures are used to:

- do the research
- oversee the research
- to see if the research was done right
- to evaluate and manage research functions.

Who may use and share information about me?

The following individuals may use or share your information for this research study:

- The Principal Investigator and the Investigator's Study team (other PA Heath System staff associated with the study).
- The Center for Precision Surgery at the University of Pennsylvania.
- The University of Pennsylvania's Institutional Review Boards (the committees charged with overseeing research on human subjects) and the University of Pennsylvania Office of Regulatory Affairs.
- The University of Pennsylvania Office of Human Research (the office that monitors research studies).

- Authorized members of the University of Pennsylvania and the University of Pennsylvania Health system and School of Medicine workforce who may need to access your information in the performance of their duties (for example, to provide treatment).

Who, outside of the School of Medicine, might receive my information?

Oversight organizations

- *The Food and Drug Administration*
- *The Office of Human Research Protections*

Once your personal health information is disclosed to others outside the School of Medicine, it may no longer be covered by federal privacy protection regulations.

The Principal Investigator or study staff will inform you if there are any additions to the list above during your active participation in the trial. Any additions will be subject to University of Pennsylvania procedures developed to protect your privacy.

How long may the School of Medicine use or disclose my personal health information?

Your authorization for use of your personal health information for this specific study does not expire.

Your information may be held in a research database. However, the School of Medicine may not re-use or re-disclose information collected in this study for a purpose other than this study unless:

- You have given written authorization
- The University of Pennsylvania's Institutional Review Board grants permission
- As permitted by law

Can I change my mind about giving permission for use of my information?

Yes. You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the investigator for the study. If you withdraw your permission, you will not be able to stay in this study.

What if I decide not to give permission to use and give out my health information?

Then you will not be able to be in this research study.

You will be given a copy of this Research Subject HIPAA Authorization describing your confidentiality and privacy rights for this study.

By signing this document, you are permitting the School of Medicine to use and disclose personal health information collected about you for research purposes as described above.

In order to protect patient privacy, once you sign informed consent you will be given a study ID number. You will be identified by your study ID number and initials listed, not your name, date of birth or medical record number. If any publications arise from this study, you will not be identified by name or any other personal identifier. The link to this data set will be maintained by the Neurosurgery Clinical Research Division in a password-protected database.

Electronic Medical Records and Research Results

What is an Electronic Medical Record?

An Electronic Medical Record (EMR) is an electronic version of the record of your care within a health system. An EMR is simply a computerized version of a paper medical record.

A clinical trial management system (CTMS) is used to register your information as a participant in a study and to allow for your research data to be entered/stored for the purposes of data analysis and any other required activity for the purpose of the conduct of the research.

If you are receiving care or have received care within the University of Pennsylvania Health System (UPHS) (outpatient or inpatient) and are participating in a University of Pennsylvania research study, results of research-related procedures (i.e. laboratory tests, imaging studies and clinical procedures) may be placed in your existing EMR maintained by UPHS. Information related to your participation in clinical research will also be contained in the CTMS.

If you have never received care within UPHS and are participating in a University of Pennsylvania research study that uses UPHS services, an EMR will be created for you for the purpose of maintaining any results of procedures performed as part of this research study. The creation of this EMR is required for your participation in this study. In order to create your EMR, the study team will need to obtain basic information about you that would be similar to the information you would provide the first time you visit a hospital or medical facility (i.e. your name, the name of your primary doctor, the type of insurance you have). Results of research procedures performed as part of your participation in the study (i.e. laboratory tests, imaging studies and clinical procedures) may be placed in this EMR.

Once placed in your EMR, these results are accessible to appropriate UPHS workforce members that are not part of the research team. Information within your EMR may also be shared with others who are determined by UPHS to be appropriate to have access to your EMR (e.g. health insurance company, disability provider, etc.).

Who can I call with questions, complaints or if I'm concerned about my rights as a research subject?

If you have questions, concerns or complaints regarding your participation in this research study or if you have any questions about your rights as a research subject, you should speak with the Principal Investigator listed on page one of this form. If a member of the research team cannot be reached or you want to talk to someone other than those working on the study, you may contact the Office of Regulatory Affairs with any question, concerns or complaints at the University of Pennsylvania by calling (215) 898-2614.

When you sign this form, you are agreeing to take part in this research study. This means that you have read the consent form, your questions have been answered, and you have decided to volunteer. Your signature also means that you are permitting the University of

Pennsylvania to use your personal health information collected about you for research purposes within our institution. You are also allowing the University of Pennsylvania to disclose that personal health information to outside organizations or people involved with the operations of this study.

A copy of this consent form will be given to you.

_____	_____	
Name of Subject (Please Print)	Signature of Subject	Date/Time
_____	_____	
Name of Person Obtaining Consent (Please Print)	Signature	Date/Time
_____	_____	
PI Name (Please Print)	PI Signature	Date/Time
_____	_____	
Name of Legal Authorized Representative (Please Print)	Signature	Date/Time