HRP-592 - Protocol for Human Subject Research with Use of Test Article(s)

Protocol Title:

SPY-X: A Study to Assess the Feasibility of Using Real-time Fluorescence Lymphangiography Alone for Sentinel Node Localization in Patients with Melanoma or Breast Cancer

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Clinicaltrials.gov Registration #:

NCT03294330.

Important Instructions for Using This Protocol Template:

1. Add this completed protocol template to your study in CATS IRB (http://irb.psu.edu) on the "Basic Information" page, item 7.
2. This template is provided to help investigators prepare a protocol that includes the necessary information needed by the IRB to determine whether a study meets all applicable criteria for approval.
3. **Type your protocol responses below the gray instructional boxes of guidance language. If the section or item is not applicable, indicate not applicable.**
4. **For research being conducted at Penn State Hershey or by Penn State Hershey researchers only, delete the instructional boxes from the final version of the protocol prior to upload to CATS IRB** (http://irb.psu.edu)**. For all other research, do not delete the instructional boxes from the final version of the protocol.**
5. When making revisions to this protocol as requested by the IRB, please follow the instructions outlined in the Study Submission Guide available in the Help Center in CATS IRB (http://irb.psu.edu) for using track changes.

If you need help…	
University Park and other campuses: Office for Research Protections Human Research Protection Program The 330 Building, Suite 205 University Park, PA 16802-7014 Phone: 814-865-1775 Fax: 814-863-8699 Email: irb-orp@psu.edu	**College of Medicine and Hershey Medical Center:** Human Subjects Protection Office 90 Hope Drive, Mail Code A115, P.O. Box 855 Hershey, PA 17033 (Physical Office Location: Academic Support Building Room 1140) Phone: 717-531-5687 Fax number: 717-531-3937 Email: irb-hspo@psu.edu

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1.0 Objectives

1.1 Study Objectives

The objective of this study is to determine if fluorescence lymphangiography can be used alone to localize sentinel nodes in patients with melanoma or breast cancer. The hypothesis is that sentinel nodes can be identified using only indocyanine green (ICG) and fluorescence lymphangiography, without the need for technetium99 and a gamma probe.

1.2 Primary Study Endpoints

The primary endpoint is the number of sentinel nodes correctly identified with ICG and fluorescence imaging alone.

1.3 Secondary Study Endpoints

Secondary endpoints include adverse events related to ICG and operative time for sentinel node biopsy.

2.0 Background

1.1 Scientific Background and Gaps

Sentinel node biopsy is a routine procedure in patients with both melanoma and breast cancer. The status of the sentinel node provides prognostic information and guides further treatment options in these patients. Sentinel node biopsy (SLN) was first developed using only a blue dye. Technetium99, a radioactive protein, was added later and provides the ability to image the patient and identify relevant lymph node basins. This feature is particularly important for trunk melanomas that can drain to multiple nodal basins. For the last 15 years or so, the standard method of SLN localization includes both tech99 and blue dye. While the rates of localization overall are excellent, these methods each have drawbacks.

Technetium 99 (tech99) is a radioactive protein that is injected dermally around the melanoma or the areola of the breast, usually one day prior to surgery. Lymphoscintigraphy is done 1-2 hours after injection and identifies the nodal basin that contains the sentinel node. Tech99 has an excellent track record of identifying sentinel nodes, but it does involve an extra trip to the hospital (patients are injected the day prior to surgery), the injection is often the most painful part of the entire treatment experience, and the signal can be vague and difficult to localize in the operating room. Furthermore, there are international concerns about the reliability of the supply of radio-labelled colloid. The reactors that currently provide tech99 and other radioactive substances are aging, and shortages of material have been threatened in the past.

Blue dye is injected dermally on the day of surgery, after the patient is anesthetized. This is a visual adjunct to the radioactive signal from the tech99. These two methods together have a success rate of approximately 96% in identifying the sentinel node. Blue dye alone localizes about 50% of sentinel nodes, and it can be problematic for the surgeon in that it stains tissues and is toxic to skin grafts.

Infrared lymphangiography using ICG and real time imaging has recently been used as an alternative method of sentinel node identification. The PI has recently completed an equivalency trial of tech99, Methylene blue (MB) and ICG. All subjects in this trial received all 3 dyes, and each was used simultaneously. In this study I found that tech99 and ICG are equivalent in their ability to localize sentinel nodes. MB was inferior to both, and I rarely use MB in my clinical practice now. With the experience and results from the first trial, the next question is whether we can use ICG and fluorescence imaging alone, without tech99 and the gamma probe. The SPY Elite and SPY PHI machines are FDA approved for perfusion imaging and are the devices used to identify the sentinel lymph nodes after injection of ICG.

2.1 Previous Data

Multiple centers have published their experience with fluorescence imaging to identify sentinel nodes, in both melanoma and breast cancer.[1-4] Ballardini et al[5] found that ICG and tech99 are equivalent in identifying sentinel nodes in patients with breast cancer, and they suggest that ICG can be used alone. In our recently completed SPY trial, 89 subjects were enrolled and received tech99, MB and ICG. The tech99 identified a mean of 1.89 sentinel nodes per patient, ICG a mean of 1.87 and MB a mean of 0.71 sentinel nodes. The ICG was well tolerated, with no adverse effects noted. A drawback to the ICG is that the fluorescent signal is visible through the skin only 47% of the time. If the nodal basin is predictable, such as for an extremity melanoma or a breast cancer, we can reasonably proceed with dissection in the predicted basin. Truncal melanomas however, do not have predictable drainage and therefore the lack of visibility is problematic for using ICG alone.

2.2 Study Rationale

There is a need to develop reliable alternatives to tech99, and there is room to improve the patient experience by eliminating unnecessary injections. Prior studies have established that ICG and fluorescence imaging can reliably detect sentinel nodes, but these studies have been performed using tech99 as well. The goal of this trial is to assess our ability to identify sentinel nodes using only ICG and fluorescence imaging. This would be a significant departure from current standard practice, thus we have included a safety mechanism in the study, which is that subjects will still receive the tech99 injection, but the surgeon is blinded to the result.

3.0 Inclusion and Exclusion Criteria

3.1 Inclusion Criteria

1. HMC, Vasser Borthers Medical Center, or Emory University School of Medicine patients with melanoma or breast cancer with planned standard of care sentinel node biopsy
   For melanoma patients, the melanoma should be located on the upper extremity between and including the wrist and shoulder, or the lower extremity between and including the ankle and groin.
2. Age: $\geq$18 years
3. Sex: Male or female
4. Fluent in written and spoken English

3.2 Exclusion Criteria

1. Melanoma located on the trunk, head or neck
2. Patient has an allergy to indocyanine green or sodium iodide
3. Pregnant or nursing women
4. Patients who have had a prior sentinel node biopsy in the same nodal basin
5. Prisoner
6. Cognitive impairment.

3.3 Early Withdrawal of Subjects

3.3.1 Criteria for removal from study

Subjects will be removed from the study if they withdraw consent prior to surgery. The study itself occurs only in the operating room, with no long term follow-up or involvement of the subject.

3.3.2 Follow-up for withdrawn subjects

Subjects will have sentinel node localization as per routine care if they withdraw from the study.

4.0 Recruitment Methods

4.1 Identification of subjects

Subjects will be identified by the PI and collaborating surgeons in clinic at HMC, Vasser Brothers Medical Center, or Emory University School of Medicine , at the time of their initial consultation.

4.2 Recruitment process

Subjects will be recruited during their initial consultation or any pre-operative visit. During this visit, routine care involves counseling the patient about melanoma or breast cancer and scheduling surgery, including the sentinel node biopsy. The surgeon usually doesn't see the patient again until the day of surgery. Subjects will not be recruited on the day of surgery.

4.3 Recruitment materials

None

4.4 Eligibility/screening of subjects

NA

5.0 Consent Process and Documentation

5.1 Consent Process

5.1.1 Obtaining Informed Consent

5.1.1.1 Timing and Location of Consent

Consent for the study would be obtained at the end of the clinic visit.

5.1.1.2 Coercion or Undue Influence during Consent

Subjects will be counseled that enrollment in the study is completely voluntary, and will not change their treatment. They will have a sentinel node biopsy whether they participate in the study or not, and the sentinel node is the same node whether it is localized with ICG or tech99. Subjects will also be counseled that they will still receive the tech99, as a backup plan in case the ICG doesn't work. They can think about the study and consent after the visit, although enrollment should occur at least 2 days prior to surgery to allow for notification of radiology not to mark the nodal basin.

5.1.2 Waiver or alteration of the informed consent requirement

A waiver of consent is requested to review medical record information to determine preliminary eligibility to participate in the research.

5.2 Consent Documentation

5.2.1 Written Documentation of Consent

The consent process will be documented in writing with the long form of consent documentation:

- The current IRB approved consent form will be obtained.
- We will verify that we are using the most current IRB-approved version of the study specific consent form and that the consent form is in language understandable to the subject/representative.
- A copy of the consent form will be provided to the subject/representative. Whenever possible the consent form will be provided to the subject/representative in advance of the consent discussion.
- If the subject/representative cannot read we will obtain an impartial witness to be present during the entire consent discussion to attest that the information in the consent form and any other information provided was accurately explained to, and apparently understood by, the subject/representative, and that consent was freely given.

5.2.2 Waiver of Documentation of Consent (Implied consent, Verbal consent, etc.)

NA

5.3 Consent – Other Considerations

5.3.1 Non-English Speaking Subjects

Non-English speaking subjects will not be enrolled.

5.3.2 Cognitively Impaired Adults

5.3.2.1 Capability of Providing Consent

NA

5.3.2.2 Adults Unable To Consent

Cognitively impaired adults will not be enrolled in the study.

5.3.2.3 Assent of Adults Unable to Consent

NA

5.3.3 Subjects who are not yet adults (infants, children, teenagers)

5.3.3.1 Parental Permission

NA. Melanoma is rare in children, and ICG is not approved for pediatric use.

5.3.3.2 Assent of subjects who are not yet adults

NA

6.0 HIPAA Research Authorization and/or Waiver or Alteration of Authorization

6.1 Authorization and/or Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

Check all that apply:

☐ **Not applicable, no identifiable protected health information (PHI) is accessed, used or disclosed in this study.** *[Mark all parts of sections 6.2 and 6.3 as not applicable]*

☐ **Authorization will be obtained and documented as part of the consent process.** *[If this is the only box checked, mark sections 6.2 and 6.3 as not applicable]*

☒ **Partial waiver is requested for recruitment purposes only (Check this box if patients' medical records will be accessed to determine eligibility before consent/authorization has been obtained).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Full waiver is requested for entire research study (e.g., medical record review studies).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Alteration is requested to waive requirement for written documentation of authorization (verbal authorization will be obtained).** *[Complete all parts of sections 6.2 and 6.3]*

6.2 Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

6.2.1 Access, use or disclosure of PHI representing no more than a minimal risk to the privacy of the individual

6.2.1.1 Plan to protect PHI from improper use or disclosure

Information is included in the Research Data Plan Form.

6.2.1.2 Plan to destroy identifiers or a justification for retaining identifiers

Study information will be retained until the sponsor notifies the study team that the information can be destroyed and all regulatory and institutional policies are met related to data retention.

6.2.2 Explanation for why the research could not practicably be conducted without access to and use of PHI

Information must be obtained from the subject's electronic medical record during recruitment to determine eligibility and, in some cases, to confirm information discussed with the subject in regards to their medical history.

6.2.3 Explanation for why the research could not practicably be conducted without the waiver or alteration of authorization

The waiver is requested only for recruitment to determine subject eligibility to ensure that no medical conditions that fall into the exclusion criteria are present and would thus preclude enrollment. This waiver will minimize the enrollment of subjects' who may ultimately fail to meet the study inclusion/exclusion criteria.

6.3 Waiver or alteration of authorization statements of agreement

Protected health information obtained as part of this research will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other permitted uses and disclosures according to federal regulations.

The research team will collect only information essential to the study and in accord with the 'Minimum Necessary' standard (information reasonably necessary to accomplish the objectives of the research) per federal regulations.

Access to the information will be limited, to the greatest extent possible, within the research team. All disclosures or releases of identifiable information granted under this waiver will be accounted for and documented.

7.0 Study Design and Procedures

7.1 Study Design

Observational pilot study.

From the subject's viewpoint, the course of events in this study will be no different than usual care and sentinel node biopsy.

7.2 Study Procedures

7.2.1 Pre-op Procedure

Subjects will have a dermal injection of technetium99 (tech99) at the melanoma tumor site prior to surgery (either the day before, or morning of surgery) or a subareolar injection if breast cancer. The surgeon will not look at the lymphoscintigraphy films, and the radiologist should not mark the skin.

7.2.2 Operative Procedure

When the subject is in the operating room and appropriately sedated or anesthetized, he or she will receive a dermal injection of indocyanine green (ICG) 0.9 ml at the melanoma tumor site or subareola if breast cancer. Incision is made in the axilla or groin, and the SPY machine is positioned over the lymph node basin. Real-time lymphangiography (SPY) is used to identify sentinel nodes. Any fluorescent nodes should be resected and are considered sentinel nodes. The absolute fluorescence will be quantified for each sentinel node. Absolute fluorescence is calculated by the SPY machine.

After the sentinel lymphadenectomy is complete but prior to closing skin, the excised lymph nodes will be examined with the gamma probe (detects tech99 signal) to confirm that they are sentinel nodes. If the node does not have a signal with the gamma probe (but is fluorescent) it is still considered a sentinel node. The lymph node basin will also be examined with the gamma probe, to insure that no sentinel nodes are missed. If a gamma positive sentinel node is identified in the lymph node basin, it should be resected and imaged with SPY. If no sentinel nodes are able to be identified with fluorescent imaging, the gamma probe will be used as per usual practice. The surgeon should spend no more than 30 minutes using SPY to identify sentinel

nodes. If after 30 minutes no sentinel node is found, the gamma probe should be used. The data collection form (separately uploaded) should be completed for each case.

7.3 Duration of Participation

Two days (pre-operative and operative procedure visits are associated with the research).

7.4 Test Article(s) (Study Drug(s) and/or Study Device(s))

7.4.1 Description

The SPY Elite machine is FDA approved for perfusion imaging. The PI has received permission from the FDA under IND number 114602 to perform this research study using a dermal injection of ICG. The ICG comes as a powder containing 25mg of indocyanine green and sterile water to reconstitute the powder for injection. Subjects will receive 2.25 mg of indocyanine green (ICG) in a volume of 0.9 mL.

7.4.2 Treatment Regimen

The patient will receive a dermal injection of indocyanine green (ICG) 0.9 mL at the melanoma tumor site or subareola if breast cancer while they are in the operating room under general anesthesia. This is a one-time injection so no dose adjustments will be made.

7.4.3 Method for Assigning Subject to Treatment Groups

This is an observational study and not a randomized trial.

7.4.4 Subject Compliance Monitoring

All pertinent procedures and data collection will occur in the operating room. Subject compliance monitoring is not applicable for this study.

7.4.5 Blinding of the Test Article

There is no blinding involved in this study.

7.4.6 Receiving, Storage, Dispensing and Return

7.4.6.1 Receipt of Test Article

ICG will be transported from the Investigational Drug Services (IDS) pharmacy to the OR pharmacy the day before surgery or the morning of the surgery depending on when the surgery is scheduled at HMC, Vasser Brother's Medical Center, or Emory University School of Medicine. The ICG will come in a 25mg vial with 10 mL of Ampule (Solvent). Subjects will receive 2.25 mg of indocyanine green (ICG) in a volume of 0.9 mL.

7.4.6.2 Storage

The ICG will be stored in the IDS pharmacy at HMC, Vasser Brother's Medical Center, or Emory University School of Medicine until the day before surgery or the morning before surgery if it is scheduled for the afternoon. A copy of the

consent form for each patient will be sent to IDS pharmacy at HMC, Vasser Brother's Medical Center, or Emory University School of Medicine prior to surgery. ICG should be stored at room temperature (between 20 – 25 degrees Celsius).

7.4.6.3 Preparation and Dispensing

The ICG will be brought from IDS pharmacy at HMC, Vasser Brother's Medical Center, or Emory University School of Medicine to the OR pharmacy the day before surgery so it is available for use the next day. If the surgery is scheduled for the afternoon then IDS pharmacy may bring the ICG over on the morning of surgery, not the day before. The surgeon will prepare the ICG and solvent for injection in the operating room prior to the start of the procedure. All aspects of the ICG preparation and use will be handled by the surgeon. Once reconstituted the ICG can be used for up to six hours, making it possible to use in several different cases in one day if the doses are drawn up in a sterile environment at the same time.

7.4.6.4 Return or Destruction of the Test Article

Any remaining ICG will be discarded in the OR at HMC, Vasser Brother's Medical Center, or Emory University School of Medicine.

7.4.6.5 Prior and Concomitant Therapy

NA

8.0 Subject Numbers and Statistical Plan

8.1 Number of Subjects

A total of 40 subjects will be recruited into this study (we estimate we will enroll 20 subjects from Penn State Hershey Medical Center and 20 between Vasser Brother's Medical Center and Emory University School of Medicine.).

The learning curve for sentinel node biopsy is 5 cases. In order to insure that the data collected accurately represents the effectiveness of the SPY machine, each surgeon will have the goal of enrolling at least 8 subjects into the study.

8.2 Sample size determination

Sample size of convenience. This is a feasibility study, and is intended to determine if fluorescence lymphangiography can be used alone to localize sentinel nodes in patients with melanoma or breast cancer. The sample size of 40 subjects is our estimation of an appropriate number of subjects such that we can draw conclusions about this technique for sentinel node biopsy, and allows sufficient numbers for multiple surgeons to be involved.

8.3 Statistical methods

The analysis of these results will be descriptive. We will assess the number of nodes per patient that are correctly identified with ICG alone, and the number of patients in whom ICG was successfully used

alone. Multiple surgeons will be involved, some with more experience than others with this technique. We will assess the learning curve by studying the success rate with ICG over time for each surgeon.

9.0 Confidentiality, Privacy and Data Management

See the attached Research Data Plan form (HRP-598)

10.0 Data and Safety Monitoring Plan

10.1 Periodic evaluation of data

Collaborating surgeons will be monitored for at least 3 subjects, or until they demonstrate proficiency with ICG and the SPY device. Proficiency of each surgeon will be assessed by the PI or a representive from Stryker prior to each surgeon enrolling patients. While observing the collaborating surgeons for training purposes, the PI or a representative from Stryker will look for competence in and understanding of the use of the SPY machine. Each surgeon should demonstrate an understanding of the images that they are looking at on the SPY machine during the procedure. After 10 subjects, the PI will review the cases to insure that sentinel nodes are being identified for each subject.

10.2 Data that are reviewed

Any adverse events that occur during surgery, whether deemed related to the ICG or not, will be reviewed. Adverse events will include reactions to ICG such as hives. Efficacy will be determined by success rates of localizing sentinel nodes with ICG alone.

10.3 Method of collection of safety information

Safety information will be collected from the collaborating surgeons, through case report forms.

10.4 Frequency of data collection

Safety data collection starts when the patient signs informed consent. Data will be collected on the day of surgery, on the standardized data collection form which is separately uploaded. Data should be forwarded to the PI within 7 business days of collection. Adverse events should be reported within 7 business days.

10.5 Individuals reviewing the data

Data will be reviewed by the PI. Adverse reactions to ICG are extremely rare, and have occurred with higher doses of ICG in subjects undergoing retinal angiography. No adverse reactions were seen in the prior study with 87 subjects, and none have been reported in the literature concerning sentinel node biopsy with ICG.

10.6 Frequency of review of cumulative data

Data will be reviewed monthly.

10.7 Statistical tests

The number of subjects planned for this study is relatively small, and given the very low complication rate seen in the prior study, statistical analysis will not be meaningful.

10.8 Suspension of research

Any grade 4 or 5 adverse event that occurs in a subject will trigger a suspension of research.

11.0 Risks

- Loss of confidentiality
- Adverse reactions to ICG are extremely rare, and none occurred in the prior trial with 87 subjects.
- Anaphylactic reactions, urticarial reactions and headache have been reported rarely in some patients.
- The risks of sentinel node biopsy are usual care as the subjects will undergo the biopsy regardless of their participation in the research. However, there is the possible risk of longer surgery, with a maximum of 30 additional minutes under anesthesia. This added time is of no consequence to the patient and carries an unmeasurable risk. Inaccurate identification of the sentinel node may occur equally in patients both on and off this study, therefore the risk in this study is no greater than usual care. The false negative rate in identifying sentinel nodes is 8%. Tech99 is used as a backup in this study in the event that the sentinel node cannot be identified with ICG.

12.0 Potential Benefits to Subjects and Others

12.1 Potential Benefits to Subjects

There are no direct benefits to the subjects.

12.2 Potential Benefits to Others

We may be able to define a group of patients who can have sentinel node localization with ICG and fluorescence imaging alone, avoiding the use of tech99. This may reduce costs, and would simplify patient care preoperatively.

13.0 Sharing Results with Subjects

Individual subjects can be told about the success of ICG during their own procedure. General study results will not be shared with subjects.

14.0 Subject Stipend (Compensation) and/or Travel Reimbursements

None

15.0 Economic Burden to Subjects

15.1 Costs

The sponsor will provide the ICG directly to HMC, Vasser Brother's Medical Center, and Emory University School of Medicine. Each institution will provide the ICG to the study patients. Subjects will be charged for Technetium 99. Subjects not enrolled in this study would be charged for blue dye, or for ICG if used in non-study patients, thus a charge for dye and injection is a usual part of the procedure.

15.2 Compensation for research-related injury

It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is

available but will be provided at the usual charge. Costs for the treatment of research-related injuries will be charged to subjects or their insurance carriers.

16.0 Resources Available

16.1 Facilities and locations

Surgical procedures will be performed at Penn State Hershey Medical Center, Vasser Brother's Medical Center, or Emory University School of Medicineas per usual care.

16.2 Feasibility of recruiting the required number of subjects

All physicians involved have an active surgical oncology practice and routinely perform sentinel node biopsy.

16.3 PI Time devoted to conducting the research

The PI has dedicated time to devote to research. Furthermore, a Human Research Technologist has been hired to assist in conducting this trial.

16.4 Availability of medical or psychological resources

All resources and facilities of HMC are available to subjects on study. In addition to the clinical team, this includes resources such as the clinical research coordinator, social workers, representatives from the American Cancer Society and various support groups for cancer or specific diseases

16.5 Process for informing Study Team

The PI or a representative from Stryker will observe three surgeries for each surgical oncologist involved in the study to ensure that they are properly trained in the use of the SPY machine. The Human Research Technologist will coordinate all communications regarding updates to the protocol.

17.0 Other Approvals

17.1 Other Approvals from External Entities

Vasser Brother's Medical Center IRB and Emory University School of Medicine IRB

17.2 Internal PSU Committee Approvals

Check all that apply:

☐ Anatomic Pathology – Hershey only – Research involves the collection of tissues or use of pathologic specimens. Upload a copy of HRP-902 - Human Tissue For Research Form on the "Supporting Documents" page in CATS IRB. This form is available in the CATS IRB Library.

☐ Animal Care and Use – All campuses – Human research involves animals and humans or the use of human tissues in animals

☐ Biosafety – All campuses – Research involves biohazardous materials (human biological specimens in a PSU research lab, biological toxins, carcinogens, infectious agents, recombinant viruses or DNA or gene therapy).

☐ Clinical Laboratories – Hershey only – Collection, processing and/or storage of extra tubes of body fluid specimens for research purposes by the Clinical Laboratories; and/or use of body fluids that had been collected for clinical purposes, but are no longer needed for clinical use. Upload a copy of HRP-901 - Human Body Fluids for Research Form on the "Supporting Documents" page in CATS IRB. This form is available in the CATS IRB Library.

☐ Clinical Research Center (CRC) Advisory Committee– All campuses – Research involves the use of CRC services in any way.

☐ Conflict of Interest Review – All campuses – Research has one or more of study team members indicated as having a financial interest.

☒ Radiation Safety – Hershey only – Research involves research-related radiation procedures. All research involving radiation procedures (standard of care and/or research-related) must upload a copy of HRP-903 - Radiation Review Form on the "Supporting Documents" page in CATS IRB. This form is available in the CATS IRB Library.

☒ IND/IDE Audit – All campuses – Research in which the PSU researcher holds the IND or IDE or intends to hold the IND or IDE.

☒ Scientific Review – Hershey only – All investigator-written research studies requiring review by the convened IRB must provide documentation of scientific review with the IRB submission. The scientific review requirement may be fulfilled by one of the following: (1) external peer-review process; (2) department/institute scientific review committee; or (3) scientific review by the Clinical Research Center Advisory committee. NOTE: Review by the Penn State Hershey Cancer Institute Scientific Review Committee is required if the study involves cancer prevention studies or cancer patients, records and/or tissues. For more information about this requirement see the IRB website at: http://www.pennstatehershey.org/web/irb/home/resources/investigator

18.0 Multi-Site Research

18.1 Communication Plans

After approval by the IRB at Penn State the protocol will be submitted for IRB approval at Vasser Brother's Medical Center and Emory University School of Medicine. Written confirmation of approval at Vasser Brother's and Emory will be required prior to enrolling subjects at these locations. All updated information regarding the protocols will be communicated to all surgical oncologists by the Human Research Technologist serving as the research coordinator for this study. Any updates to the consent form will result in the HRT sending an updated copy of the form along with a follow up phone call to confirm that the newest version of the form will be used with all subsequent patients. New information will be communicated via email and receipt will be confirmed by the use of the vote function. All pertinent communications will be followed up with a phone call to ensure compliance.

18.2 Data Submission and Security Plan

A REDCap database will be developed in order to store the collected information. All enrollment, consent and data collection forms from Vasser Brother's and Emory will be scanned and emailed to the Human Research Technologist at Penn State Hershey. Files will be sent using the Penn State Hershey Secure File Transfer application known as Accellion. This application will allow files to be sent and received from Vasser Brother's and Emory in a secure manner. The hard copy will be kept in a locked file in the clinical trials office at Vasser Brother's and Emory, until the study has closed and the manuscript accepted for publication. Files can then be destroyed. Documents should be scanned and emailed as soon as they are completed.

18.3 Subject Enrollment

Subjects will be enrolled during their normally scheduled visit with the surgical oncologist. The study is not randomized, and subjects do not need to be coordinated in relation to other subjects.

18.4 Reporting of Adverse Events and New Information

All adverse events will be reported to the PI within seven days of occurrence. New information will be communicated via email and receipt will be confirmed by the use of the vote function. All pertinent communications will be followed up with a phone call to ensure compliance.

18.5 Audit and Monitoring Plans

All surgeons will be monitored by the PI or a representative from Stryker for a minimum of three cases with the SPY machine. The data collection form will be approved by all physicians prior to the start of the study. After enrolling each patient an analysis of the data forms will be done and the quality of the data collection forms will be reviewed.

19.0 Adverse Event Reporting

19.1 Adverse Event Definitions

Adverse event	Any untoward medical occurrence associated with the use of the drug in humans, whether or not considered drug related
Adverse reaction	Any adverse event caused by a drug
Suspected adverse reaction	Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than "adverse reaction". • *Reasonable possibility.* For the purpose of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event.
Serious adverse event or Serious suspected adverse reaction	Serious adverse event or Serious suspected adverse reaction: An adverse event or suspected adverse reaction that in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
Life-threatening adverse event or life-threatening suspected adverse reaction	An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator (i.e., the study site principal investigator) or Sponsor, its occurrence places the patient or research subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that had it occurred in a more severe form, might have caused death.

Unexpected adverse event or Unexpected suspected adverse reaction.	An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure, general investigational plan, clinical protocol, or elsewhere in the current IND application; or is not listed at the specificity or severity that has been previously observed and/or specified.

For device studies, incorporate the following definitions into the below responses, as written:	
Unanticipated adverse device effect	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or IDE application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

19.2 Recording of Adverse Events

All adverse events (serious or non-serious) and abnormal test findings observed or reported to study team believed to be associated with the study drug(s) or device(s) will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator.

An abnormal test finding will be classified as an adverse event if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy
  NOTE: Simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an adverse event.
- The test finding leads to a change in study drug dosing or discontinuation of subject participation in the clinical research study

The test finding is considered an adverse event by the investigator.

19.3 Causality and Severity Assessments

The investigator will promptly review documented adverse events and abnormal test findings to determine 1) if the abnormal test finding should be classified as an adverse event; 2) if there is a reasonable possibility that the adverse event was caused by the study drug(s) or device(s); and 3) if the adverse event meets the criteria for a serious adverse event.

If the investigator's final determination of causality is "unknown and of questionable relationship to the study drug(s) or device(s)", the adverse event will be classified as associated with the use of the study drug(s) or device(s) for reporting purposes. If the investigator's final determination of causality is "unknown but not related to the study drug(s) or device(s)", this determination and the rationale for the determination will be documented in the respective subject's case history.

19.4 Reporting of Adverse Reactions and Unanticipated Problems to the FDA

19.4.1 Written IND/IDE Safety Reports

The Sponsor-Investigator will submit a written IND Safety Report (i.e., completed FDA Form 3500A) to the responsible new drug review division of the FDA for any observed or volunteered adverse event that is determined to be a serious and unexpected, suspected adverse reaction. Each IND Safety Report will be prominently labeled, "IND Safety Report", and a copy will be provided to all participating investigators (if applicable) and sub-investigators.

Written IND Safety Reports will be submitted to the FDA as soon as possible and, in no event, later than 15 calendar days following the Sponsor-Investigator's receipt of the respective adverse event information and determination that it meets the respective criteria for reporting.

For each written IND Safety Report, the Sponsor-Investigator will identify all previously submitted IND Safety Reports that addressed a similar suspected adverse reaction experience and will provide an analysis of the significance of newly reported, suspected adverse reaction in light of the previous, similar report(s) or any other relevant information.

Relevant follow-up information to an IND Safety Report will be submitted to the applicable review division of the FDA as soon as the information is available and will be identified as such (i.e., "Follow-up IND Safety Report").

If the results of the Sponsor-Investigator's follow-up investigation show that an adverse event that was initially determined to not require a written IND Safety Report does, in fact, meet the requirements for reporting; the Sponsor-Investigator will submit a written IND Safety Report as soon as possible, but in no event later than 15 calendar days, after the determination was made.

19.4.2 Telephoned IND Safety Reports – Fatal or Life-threatening Suspected Adverse Reactions

In addition to the subsequent submission of a written IND Safety Report (i.e., completed FDA Form 3500A), the Sponsor-Investigator will notify the responsible review division of the FDA by telephone or facsimile transmission of any unexpected, fatal or life-threatening suspected adverse reaction.

The telephone or facsimile transmission of applicable IND Safety Reports will be made as soon as possible but in no event later than 7 calendar days after the Sponsor-Investigator's receipt of the respective adverse event information and determination that it meets the respective criteria for reporting.

19.5 Reporting Adverse Reactions and Unanticipated Problems to the Responsible IRB

In accordance with applicable policies of The Pennsylvania State University Institutional Review Board (IRB), the investigator will report, to the IRB, any observed or reported harm (adverse event) experienced by a subject or other individual, which in the opinion of the investigator is determined to be (1) unexpected; and (2) probably related to the research procedures. Harms (adverse events) will be submitted to the IRB in accordance with the IRB policies and procedures.

19.6 Unblinding Procedures

NA

19.7 Stopping Rules

NA

20.0 Study Monitoring, Auditing and Inspecting

20.1 Study Monitoring Plan

20.1.1 Quality Assurance and Quality Control

The study will be monitored by the Clinical Trial Monitoring Team from the Department of Public Health Sciences at Penn State Hershey College of Medicine. The monitors will provide an independent review of the regulatory and subject records and the data collected to assure compliance with the protocol, GCP, and applicable federal regulations. The monitoring will occur at regular intervals after the enrollment of the first subject and the times will be predetermined by the monitoring plan developed by the Clinical Trial Monitoring Team.

20.1.2 Safety Monitoring

The **Principal Investigator** will confirm that all adverse events (AE) are correctly entered into the AE case report forms by the coordinator; be available to answer any questions that the coordinators may have concerning AEs; and will notify the IRB, FDA, sponsor and/or DSMB of all applicable AEs as appropriate. All assessments of AEs will be made by a licensed medical professional who is an investigator on the research.

21.0 Future Undetermined Research: Data and Specimen Banking

21.1 Data and/or specimens being stored
NA

21.2 Location of storage
NA

21.3 Duration of storage
NA

21.4 Access to data and/or specimens
NA

21.5 Procedures to release data or specimens
NA

21.6 Process for returning results
NA

22.0 References

1. Cloyd JM, Wapnir IL, Read BM, Swetter S, Greco RS. Indocyanine green and fluorescence lymphangiography for sentinel lymph node identification in cutaneous melanoma. *Journal of surgical oncology.* Dec 2014;110(7):888-892.

2. Fujisawa Y, Nakamura Y, Kawachi Y, Otsuka F. Indocyanine green fluorescence-navigated sentinel node biopsy showed higher sensitivity than the radioisotope or blue dye method, which may help to reduce false-negative cases in skin cancer. *Journal of surgical oncology.* Jul 1 2012;106(1):41-45.

3. Hirche C, Murawa D, Mohr Z, Kneif S, Hunerbein M. ICG fluorescence-guided sentinel node biopsy for axillary nodal staging in breast cancer. *Breast cancer research and treatment.* Jun 2010;121(2):373-378.

4. Stoffels I, Dissemond J, Poppel T, Schadendorf D, Klode J. Intraoperative Fluorescence Imaging for Sentinel Lymph Node Detection: Prospective Clinical Trial to Compare the Usefulness of Indocyanine Green vs Technetium Tc 99m for Identification of Sentinel Lymph Nodes. *JAMA surgery.* Jul 2015;150(7):617-623.

5. Ballardini B, Santoro L, Sangalli C, et al. The indocyanine green method is equivalent to the (9)(9)mTc-labeled radiotracer method for identifying the sentinel node in breast cancer: a concordance and validation study. *European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology.* Dec 2013;39(12):1332-1336.