PROTOCOL TITLE: *A pilot study to evaluate single dose indocyanine green 24 hours prior to operative treatment of orthopaedic infection.*

D-HH IRB OVERSIGHT:

One of the following must be true in order to submit to the D-HH IRB. Please check all that apply:

☒ The Principal Investigator is employed by D-H
☒ The study will utilize any D-H data or specimens
☒ The study will enroll D-H patients or recruit from D-H sites
☒ The study will utilize any D-H resources, e.g. study procedures will occur at D-H locations and/or use of D-H equipment or shared resources

PROTOCOL TITLE:

A pilot study to evaluate single dose indocyanine green 24 hours prior to operative treatment of orthopaedic infection.

PRINCIPAL INVESTIGATORs:

Ida Leah Gitajn
Orthopaedics
603-650-5133
Ida.leah.gitajn@hitchcock.org

VERSION NUMBER/DATE:

Version 2: October 26, 2022

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1	04Feb2022	Dosing of ICG in CRU	Yes
2	26Oct2022	Removing Dr. Jevsevar	Yes

PROTOCOL TITLE: *A pilot study to evaluate single dose indocyanine green 24 hours prior to operative treatment of orthopaedic infection.*

Table of Contents

1.0 Study Summary

Study Title	A pilot study to evaluate single dose indocyanine green 24 hours prior to operative treatment of orthopaedic infection.
Study Design	Prospective Observational Trial
Primary Objective	The primary study objective is to explore the variability associated with bone and soft tissue perfusion in infection patients, using ICG fluorescence imaging.
Secondary Objective(s)	The secondary study objective is to evaluate the change in single dose, 24h ICG distribution from pre to post debridement.
Research Intervention(s)/ Investigational Agent(s)	Indocyanine green (ICG)-based dynamic contrast enhanced fluoresce imaging (diagnostic test)
IND/IDE #	N/A
Study Population	Patients 18 years of age or older who present to DHMC with an orthopaedic infection
Sample Size	20 patients
Study Duration for individual participants	6 months
Study Specific Abbreviations/ Definitions	CDC: Centers for Disease Control and Prevention CRU: Clinical Research Unit CRF: Case Report Forms DCE-FI: Dynamic Contrast Enhanced Fluorescence Imaging D-HH HRPP: Dartmouth-Hitchcock Human Research Protection Program DHMC: Dartmouth Hitchcock Medical Center FI: fluorescence imaging GCP: Good Clinical Practice GFR: glomerular filtration rate ICG: Indocyanine Green NSF: nephrogenic sclerosing fibrosis ROI: Region of interest SSI: Surgical Site Infection

Objectives*

The primary study objective is to explore the variability associated with bone and soft tissue perfusion in infection patients, using ICG fluorescence imaging.

The secondary study objective is to evaluate the change in single dose, 24h ICG distribution from pre to post debridement.

The third study objective is to preliminarily determine whether a single dose of ICG given 24h preoperatively can predict recurrent infection/treatment failure

2.0 Background*

The focus of this study is to (1) Explore variability in distribution of 24h ICG in bone and soft tissue infection (2) Evaluate the change in 24h ICG distribution from pre to post debridement (3) Preliminarily determine whether 24h ICG has the possibility predict infection / treatment failure

Infection following trauma is one of the most prevalent and challenging complications faced by orthopedic surgeons in both military and civilian populations, occurring after up to 60% of open bone fractures[1-7]. Several factors specific to this trauma place patients at high risk for infectious complications, including: traumatized tissues, open contaminated fracture, soft tissue coverage issues, catabolic state due to poly-trauma, prolonged hospitalization with exposure to nosocomial bacteria, and presence of metallic implants[8]. Infection requires one or more unplanned surgical procedures and leads to prolonged morbidity, loss of function, and potential loss of limb[1, 9-11]. Failed treatment for bone infection results in recurrent infection, requiring repeat surgical procedures in approximately 30% of patients.[12-15]

We are currently enrolling patients into a study to evaluate the utility of first window ICG to identify areas of deficient perfusion. This is based upon the concept deficient perfusion prevents delivery of antibiotics and endogenous immune cells to traumatized tissues. In the setting of established infection, poorly perfused bone can be a nidus for biofilm formation creating resistance to antibiotics. However, in the context of this work it is becoming increasingly clear that acute (rather than chronic) infections display hyper vascularity with increased blood flow and neovascularization. Infection is known to display the enhanced permeability and retention effect with increased vascular permeability. Second window or 24h ICG represents an ideal method to identify these areas of increased vascular permeability. In some instances infected tissue can be hard to distinguish from healthy

tissue when ICG is given immediately before optical imaging Second window ICG will allow surgeons to better distinguish infected tissue from healthy tissue as the ICG will have a better opportunity to permeate the infected tissue while it will have been expelled from the health tissue.

There are currently no accepted intraoperative tools that can be used to make objective decisions about which bone and tissue is infected and which is normal. Methods currently used to guide debridement are quite rudimentary. Clinical judgement is based on the gross appearance of soft tissue and bone, including color, turgor, and extent of soft tissue stripping. A burr may be used to look for bleeding bone. More extensive debridement is thought to minimize risk of index infection or reduce the rate of persistent infection; however, this comes at the cost of increasingly complex reconstructive procedures to fill bony defects[22, 23, 24]. Clearly what is needed is a functional imaging system which can identify infected tissues to guide surgeons in the amount of tissue to debride. In turn, this will lead to fewer infections and a more effective treatment of SSIs at the fracture site. Both scenarios will allow patients to return to duty or work sooner.

3.0 Study Endpoints*

The study endpoint is to determine the variability of bone and soft tissue perfusion in infection patients when given a single dose of ICG 24h prior to surgical debridement. The long term goal of this study is to aid in the development and optimization of bone specific imaging strategies that can be used to guide debridement and to optimize the quality of bone / tissue resection to minimize complications.

4.0 Study Intervention/Investigational Agent

1. **Description:** This study is neither a drug nor a device trial. Patients will be administered FDA approved ICG through intravenous injection and imaged by either a FDA approved surgical fluorescence imaging device (Spy Elite) or the Zeiss Penero 800 both of which are held approximately 0.5 meter away from the subject. ICG fluorescence and both the Spy elite imaging system and the Zeiss Penero 800 surgical microscope have been used for routine clinical practice for many years. ICG fluorescence imaging utilizes intravenously injected ICG, which is a fluorescent dye that is FDA-approved for clinical use, illuminated with near-infrared light. The ICG dye is indirectly activated and the dynamic fluorescence due to bone perfusion can be captured by a video rate imaging system.

2. **Drug/Device Handling:** Indocyanine green (ICG) study medication will be ordered and stored by the investigational pharmacy for administration pre operatively.

   ICG is FDA approved for routine clinical practice. No return or destruction of study drug is needed for this study.

3. **Dose Rationale:** We plan a sample size of 20 patients in this open label prospective observational study of ICG fluorescence imaging for patients with orthopaedic infection No randomization will be performed. For each patient enrolled in the study 2.5 - 5mg/kg ICG will be injected intravenously 24h prior to surgical debridement. Previous studies by John Lee, MD have indicated that the upper range of the dose may be necessary to obtain acceptable imaging (letter of support attached). ICG fluorescence images will be acquired pre and post-surgical debridement.

5.0 Procedures Involved*

Eligible patients regardless of ethnicity or health status, will be identified and recruited subject to inclusion and exclusion criteria above. Patients who meet eligibility criteria will be asked to participate in the trial. If they agree, written informed consent will be obtained from the patient or their healthcare proxy. To obtain informed consent, study personnel (surgeon or research coordinator) will adhere to the following procedures: (1) present study information in a manner that is understandable to the patient; (2) discuss the study with the patient and answer any questions; (3) allow the patient an opportunity to discuss participation with their family; (4) confirm that the patient understands the risks and benefits of participating in the study and that their participation is voluntary; (5) complete the consent process and obtain signatures from the patient and research team. The process of obtaining and documenting informed consent forms will be completed in accordance with local Good Clinical Practice (GCP) recommendations.

If the research team member obtaining consent is at all unsure about the patient's ability to consent, s/he will consult with the study PI.

This study seeks to include individuals with lacking or limited decision making capacity. A legally authorized representative (LAR) with reasonable knowledge of the potential participant will be approached to consent on the patient's behalf if the patient cannot adequately answer at least 2 questions about the study, or it is determined that the patient's level of cognition is not likely to change before study medication (ICG) can be administered . These questions will be to assess the participant's understanding of the study and

what it means to participate, their appreciation of the consequences of participation, and their ability to consider alternatives to participation.

The choice of LAR will follow standard procedures. The following with be approached in this order of priority:

- Legal guardian
- Proxy (health care agent) named in an advance directive or durable power of attorney for health care;
- Family member or other surrogate identified by the state law on health care decisions.

Guidance will be provided to assist the LAR in making the consent decision. They will advised to base the decision on the participant's expressed wishes, or, if these are not known, what they believe the participant would have desired under the circumstances of the injury, their beliefs and values. If the LAR does not know what the participant would have wanted, the LAR will advised to base the decision with the participant's best interest in mind. They will be asked to carefully consider how much leeway the participant would likely give the LAR in making the choice about participation in the study.

Recognizing that consent is an ongoing process, the study team will encourage the participants to ask additional questions that may arise during the course of their participation in the study.

If the patient is inpatient at the time of ICG administration then no additional IV access will need to be obtained. If the patient is dosed with ICG in the CRU then a qualified member of the CRU staff will insert the IV and then remove it before the patient leaves the CRU.

Patients will be administered a single, ICG, 2.5-5mg/kg dose 24 hours prior to surgery by a qualified member of their care team. The patient will be prepared and transported to surgery as per routine at Dartmouth-Hitchcock. In the OR, patient positioning, preparation of the surgical field, and draping will follow standard practice, of fracture fixation or joint fusion or requiring open surgical debridement/saucerization for osteomyelitis.

ICG fluorescence images will be acquired prior to surgical debridement. Debridement will then proceed per standard of care. The wound will be irrigated with a minimum of 3 liters irrigation with normal saline. After irrigation and debridement is completed another ICG fluorescence image will be acquired.

Costs associated with the purchase and administration of ICG will be billed directly to the study. Neither the patient or their health insurance provider will be responsible for any costs associated with the imaging procedures or the ICG administrations. The patient and / or their insurance company will be billed for a pregnancy test as part of routine surgery precautions for women of childbearing potential.

The need for repeat debridement or tissue cultures will be left up to the treating surgeon. If repeat debridement is needed, pre- and post-debridement quantitative ICG fluorescence images will be obtained at each procedure. In the situation where a debridement surgery is repeated on another date, the subject will undergo consent as outlined in the protocol for each additional surgery for which imaging will be obtained. If the skin wound is unable to be closed, it will be left open with a sterile dressing until delayed coverage in collaboration with plastic surgery.

ICG will be administered by a qualified member of the care team. During administration patients will either be under the care and observation of the inpatient care teams or closely monitored by a qualified member of the CRU for at least 30 minutes post ICG administration. Postoperatively, patients are transferred to the Post-Anesthesia Care Unit (PACU) where they are monitored continuously by nursing staff supervised by anesthesiologists. During this entire time vital signs (including temperature, pulse, respiratory rate and blood pressure) are collected as standard of care. All clinical data will be reviewed for adverse events for a period of 24 hours post-injection by members of the care team.

Day of Injection Procedures	Pre- Infusion	Up To 24 Hours Post Injection
Pulse	X	X
Blood Pressure	X	X
Temperature	X	X
Respiratory Rate	X	X
Adverse Events		X

Upon admission and throughout the hospital course, patients will be treated with antibiotics per standard of care by the orthopaedic service or in collaboration with infectious disease recommendations. Management of study patients including clinical and radiographic assessments will not differ from standard of care.

Study participants will be followed for a period of 6 months following injection of 24h ICG. Final follow-up will be at 6 months to capture all infectious complications (Figure C.2)[35]. If a participant does not return to clinic, follow-up may be conducted by telephone. SSI and unplanned fracture-related reoperations will be identified at the time of diagnosis/occurrence and/or during each participant clinical assessment and medical record review that will occur during their routine outpatient clinic visits.

Figure C.2 follow up assessments

Assessment	Visit 1: Enrollment	Visit 2: 6 months
Eligibility Screening	●	
Informed Consent	●	
Collection of Demographic and Fracture/Infection Data	●	
Collection of Surgical Data	●	
Collection of Peri-Operative Data	●	
Collection of Outcome Data		●
Collection of Serious Adverse Events	●	●

6.0 Data and Specimen Banking*

Not Applicable

7.0 Sharing of Results with Subjects*

Results will not be shared with subjects or others associated with the subject's medical care

8.0 Study Timelines*

All patients will participate in the following events shown in Table C.2. Follow up visits will be conducted during standard postoperative clinical visits or over the phone.
We anticipate enrolling patients for 4 years with an additional 6 months needed to complete 6-month follow-up for all patients. We anticipate completing primary analyses at the end of 6 month follow-ups.

9.0 Inclusion and Exclusion Criteria*

Inclusion Criteria

1. Patients 18 years of age or older.
2. Extremity fracture.
3. Prior definitive fracture management with external fixation, internal fixation, or joint fusion.
4. Superficial, deep, or organ space SSI (as per CDC criteria) at the fracture site that requires operative management.
5. Will have all planned SSI care surgeries performed by a participating surgeon or delegate.
6. Provision of informed consent.

Exclusion Criteria

1. Fractures of the hand cannot be imaged.
2. Iodine allergy.
3. Burns at the SSI site.
4. Incarceration.
5. Expected survival of less than 90 days.
6. Problems, in the judgment of study personnel, with maintaining follow-up with the patient.
7. Adults unable to consent or whom do not have a LAR
8. Individuals who are not yet adults (infants, children, teenagers)
9. Pregnant or breastfeeding women

10.0 Vulnerable Populations*

In order to ensure that this study is not biased against patients with the most severe infections, who are most likely to benefit from this imaging device, patients who are cognitively impaired (most likely due to head trauma) will be eligible for this study.

A legally authorized representative (LAR) with reasonable knowledge of the potential participant will be approached to consent on the patient's behalf if the patient cannot adequately answer at least 2 questions about the study or it is determined that the patient's level of cognition is not likely to change before study medication (ICG) can be administered . These questions will be to assess the participant's understanding of the study and what it means to participate, their appreciation of the consequences of participation, and their ability to consider alternatives to participation.

The choice of LAR will follow standard procedures. The following with be approached in this order of priority:

- Legal guardian
- Proxy (health care agent) named in an advance directive or durable power of attorney for health care;
- Family member or other surrogate identified by the state law on health care decisions.

Guidance will be provided to assist the LAR in making the consent decision. They will advised to base the decision on the participant's expressed wishes, or, if these are not known, what they believe the participant would have desired under the circumstances of the injury, their beliefs and values. If the LAR does not know what the participant would have wanted, the LAR will advised to base the decision with the participant's best interest in mind. They will be asked to carefully consider how much leeway the participant would likely give the LAR in making the choice about participation in the study.

This is in compliance with Checklist HRP-417 (Cognitively Impaired Adults).

11.0 Local Number of Subjects

This is a pilot study to investigate the feasibility of obtaining fluorescence imaging following injection of ICG 24 hours prior to surgery for infection. This study seeks to enroll 20 patients. Several studies by this investigator inject ICG during surgery, however none have investigated ICG injection prior to surgery. The data collected in this pilot study will inform future studies involving ICG injection and the optimal time of injection.

12.0 Recruitment Methods

Participation in this research requires informed consent according to Institutional Review Board (IRB) guidelines and a signed IRB-approved Consent Form as the means of documenting this understanding.

Potential subjects will be identified either through the Orthopaedic outpatient clinic or by the patient's primary attending when the patient is currently an in-patient. Subjects who have undergone previous trauma surgeries and have developed an infection will be assessed for protocol inclusion criteria. This study requests a partial waiver of HIPAA for recruitment purposes. The partial waiver would allow for the surgeon to share with the research coordinator the patient name, sex, MRN number, age, underlying conditions as well as type and location of injury. There is an adequate plan to protect identifiers from improper use and disclosure as

information will only be used by study team members to determine whether a patient may be eligible. Information will only be communicated and stored using D-HH approved secure platforms. Information is only being used to determine if a patient is eligible for the study, for recruitment purposes. Once approached, if a patient is not interested, information will be destroyed. Protected health information will not be re-used or disclosed for another purpose. It will only be used for recruitment. This research could not practically be done without a partial waiver of HIPAA. This information is needed for recruitment. Patients will sign a full HIPAA Authorization when consenting to the study.

Subjects will be invited to participate in this study by a member of the orthopaedic care team, which will occur either at the time of consultation with the surgeon about the candidate's standard-of-care procedures or at another time agreed to by the potential participant, the candidate's surgeon or their designee. No advertisements or other promotional material will be used. No finder fees or recruitment incentives will be offered. Women of child bearing potential are eligible for enrollment into this study because ICG administration is not considered to present any additional risk for these women. The study will exclude women who are pregnant or breast-feeding as indicated in the exclusion criteria. Women of child-bearing potential, if asked to participate, will be given a pregnancy test as part of their standard of care testing prior to surgery and before administration of ICG.

All follow-up visits are within standard practice for these injuries/diagnoses.

Several additional strategies may be used to maximize follow-up including: 1) at the time of enrollment each participant will provide their own telephone number, as well as the name and address of a primary care physician, and the names and phone numbers of three people at different addresses with home the participant does not live and who are likely to be aware of the patient's whereabouts; 2) participants will receive a reminder card upon discharge for their next follow-up visit by the clinical staff; 3) participants who opt to receive text message reminders, will be given text message reminders; 4) follow-up will coincide with normal surgical infection clinic visits; and 5) if a participant refuses or is unable to return for the follow-up assessment, study personnel will determine his/her status with regards to major study outcomes by telephone.

13.0 Withdrawal of Subjects*

Participants will be removed from the protocol if:

- Study imaging is not completed for any reason.
- The subject withdraws consent.
- The subject has an occurrence of a significant clinical event that precludes imaging.

- The subject becomes pregnant before injection of ICG

If a participant is withdrawn from the protocol, the PI will mark the data of this subject as "withdrawn" and will add a detailed explanation about the cause of withdrawal in the database.

Subjects who withdraw after intraoperative imaging will be informed that data already collected may not be removed from the study database. Subjects will be asked if they would be willing to allow the investigator to collect data from their routine medical care. If the patient agrees then the research coordinator will collect follow up data from the electronic medical record at each follow up visit pertaining to the injury. The data collected will then be used in the statistical analysis portion that only involves the intraoperative image data and infection status. Those who do not wish to allow the investigator collect data from their electronic medical record will be asked to submit this request in writing to the investigator or a member of the research team.

14.0 Risks to Subjects*

The risks to subjects are minimal in relation to anticipated benefits and/or knowledge that might reasonably be expected from the results of this clinical trial.

Risk of ICG injection: ICG (Indocyanine Green) will be administered intravenously once, 24h preoperatively. ICG is FDA approved for human use in angiography for ophthalmology and cardiology applications and is given routinely to patients in these clinical settings. The risks are considered minimal and consist of nausea, vomiting, hives, increased heart rate in subjects with particular sensitivity to the dye. ICG does contain sodium iodide and patients with a history of allergy to iodides will be excluded. Anaphylactic or urticardial reactions are rare but have been reported in patients both with and without a history of allergy to iodides. Anaphylactic deaths have been reported following IGG administration during cardiac catheterization. Reported rates of mild, moderate and severe adverse reactions to ICG are 0.15%, 0.2% and 0.05%. Every effort will be made to minimize this risk as much as possible. It is the standard of care at this institution to obtain information related to allergies, sensitivities and past medical histories upon patient arrival. Patients will also be monitored throughout their hospitalization, as is the standard of care, by everyone involved in their medical care for evidence of new or previously unknown reactions or sensitivities. Additionally, at all times ICG fluorescence imaging assessments are taking place, research staff and both surgical and anesthesia staff will monitor patients closely for any adverse reaction to ICG. Qualified inpatient medical staff or CRU staff will monitor patients for at least 30

minutes after ICG fluorescence injection has been completed. In the event of an unexpected allergic reaction, Dartmouth-Hitchcock Medical Center and all affiliated groups within this institution have procedures in place for managing patients with unknown or unexpected allergic reactions. If such a reaction were to occur, all standard of care treatments will be provided including but not limited to treatment with appropriate agents such as epinephrine, antihistamines and corticosteroids. Risk of infection from IV injection is also extremely rare but can occur. Pregnant women are excluded from the study. A pregnancy test is administered to women of child-bearing age on request at no cost.

Risk of infection from IV injection is extremely rare but can occur.

Prolonged operating room time: Because the ICG fluorescence assessments will take place in the operating room, participation in this study may increase the amount of time spent under surgical anesthesia in the operating room. For the average case, an additional 10 minutes at most will be incurred. However, the research staff will make every effort to minimize this risk by performing the assessment test while other required operative procedures are being performed.

Risk of confidentiality breach: Subjects enrolled in research are always exposed to additional risks of a breach in confidentiality, for example, of some elements of their personal health information that is made available to study investigators as part of their participation. The risk is 100%, but the occurrence rate of an actual breach is < 1% (to date, we are not aware of any subject participating in our studies who has experienced a detrimental breach of confidentiality or confidential information).
Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Risk of breach of confidentiality of the medical records and status of participants will be minimized. Databases which are used to store subject-sensitive information are password-protected and encrypted during file/data transfers from viewing terminals. Access will be limited to research team members who have undergone CPHS training at Dartmouth. Whenever possible and practical standard-of-care clinical data used in the research will be de-identified when under analysis.

15.0 Potential Benefits to Subjects*

Patients enrolling in this study will not benefit directly because no diagnostic or therapeutic decisions will occur based on the study, and thus, administration of the study is not intended to alter the surgical procedure. However, future patients may

benefit from the knowledge gained from the study since this study may provide an objective, intraoperative, and real-time methodology to assess bone perfusion and thoroughness of debridement. This method may save the patients from unnecessarily high risk for index infection or nonunion—in the setting of open fracture—or recurrent infection in the setting of established infection, due to the substantial practice variation.

16.0 Data Management* and Confidentiality

Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Risk of breach of confidentiality of the medical records and status of participants will be minimized. Databases which are used to store subject-sensitive information are password-protected and encrypted during file/data transfers from viewing terminals. Access will be limited to research team members who have undergone CPHS training at Dartmouth. Whenever possible and practical standard-of-care clinical data used in the research will be de-identified when under analysis. All data will be communicated in a HIPAA-compliant manner using a HIPAA-compliant database for clinical data (REDCap) and a HIPAA-compliant storage drive for imaging data. Clinical and imaging data will be uploaded to the appropriate HIPAA-compliant site by the local research team at each institution and all data will be analyzed at either Dartmouth Hitchcock Medical Center or Dartmouth College/Thayer School of Engineering. De-identified patient information using a Study ID number will be utilized whenpossible.

Case Report Forms: Study case report forms (CRFs) will be the primary data collection instruments for the study. All data requested on CRFs will be recorded. Any missing data will be explained. If a space on the CRF is left blank because the procedure was not performed or the question was not asked, a written notation will be made. If an item is not applicable to an individual case, written notation will be made. Changes to the CRFs will be initialed and dated.

Record Retention: Following closure of the study, the investigator will maintain all site study records in a safe and secure location. The records are maintained to allow easy and timely retrieval when needed (e.g., audit or inspection) and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and staff. Upon completion of study analysis, research information is stored off site in accordance with the D-HH policy for retention of study records.

17.0 Provisions to Monitor the Data to Ensure the Safety of Subjects*

Clinical research monitoring for regulatory compliance and data integrity will be conducted. Internal monitoring is conducted by appropriately trained staff of the Office of Clinical Research and Dartmouth- Hitchcock Medical Center Clinical Trials Office who are not involved in the study. This monitoring will include periodic assessment of the regulatory compliance, data quality, and study integrity. Study records will be reviewed and directly compared to source documents and the conduct of the study will be discussed with the investigator. Monitors may request access to all regulatory documents, source documents, CRFs, and other study documentation for on-site inspection. Direct access to these documents is guaranteed by the investigator, who must provide support at all times for these activities.

18.0 Provisions to Protect the Privacy Interests of Subjects

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Risk of breach of confidentiality of the medical records and status of participants will be minimized. Databases which are used to store subject-sensitive information are password-protected and encrypted during file/data transfers from viewing terminals. Access will be limited to research team members who have undergone CPHS training at Dartmouth. Whenever possible and practical standard-of-care clinical data used in the research will be de-identified when under analysis. All data will be communicated in a HIPAA-compliant manner using a HIPAA-compliant database for clinical data (REDCap) and a HIPAA-compliant storage drive for imaging data. Clinical and imaging data will be uploaded to the appropriate HIPAA-compliant site by the local research team at each institution and all data will be analyzed at either Dartmouth Hitchcock Medical Center or Dartmouth College/Thayer School of Engineering. De-identified patient information using a Study ID number will be utilized whenpossible.

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their

participation in this study. See Attachment for a copy of the Subject Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the IRB. The formal consent of a subject, using the IRB-approved consent form, will be obtained before that subject undergoes any study procedure. The consent form will be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

19.0 Compensation for Research-Related Injury

If in any case subjects are injured or become ill as a result of research procedures, the subjects will be provided with medical treatment, but the following organizations do not plan to pay for this treatment.

- Mary Hitchcock Memorial Hospital
- Dartmouth-Hitchcock Clinic
- Dartmouth-Hitchcock Medical Center
- Trustees of Dartmouth College

20.0 Economic Burden to Subjects

There are no additional costs that subjects will accrue in association with participating in this research. Costs associated with the purchase and administration of ICG will be billed directly to the study. Neither the patient or their health insurance provider will be responsible for any costs associated with the imaging procedures or the ICG administrations. The patient and / or their insurance company will be billed for a pregnancy test as part of routine surgery precautions for women of childbearing potential. All follow-up visits will be conducted during standard of care follow-up visits or over the phone. Costs associated with the ICG and imaging device will be covered by the study and will not be billed to the patient.

21.0 Consent Process

To obtain informed consent, study personnel will adhere to the following procedures: (1) present study information in a manner that is understandable to the patient; (2) discuss the study with the patient and answer any questions; (3) allow the patient an opportunity to discuss participation with their family; (4) confirm that the patient understands the risks and benefits of participating in the study and that their participation is voluntary; and (5) complete the consent process and obtain signatures from the patient and research team. The process of obtaining and documenting informed consent will be completed in

accordance with Good Clinical Practice. If the research team member obtaining consent is at all unsure about the patient's ability to consent, s/he will consult with the study PI.

Recognizing that consent is an ongoing process, the study team will encourage the participants to ask additional questions that may arise during the course of their participation in the study.

This study will not involve the subjects who is under age 18.

The study team will comply with consent procedures outlined in SOP HRP-090.

Cognitively Impaired Adults
This study does not involve the assessment of an experimental treatment to the subjects enrolled. The subjects will undergo a method for collecting imaging data that has been fully vetted and utilized in other clinical settings. The purpose of this research it to evaluate the utility of this imaging technique in orthopaedic trauma patients who have developed an infection.

By virtue, as a result of high energy trauma that often precedes orthopaedic surgical site infections some percentage of the patients will have diminished cognitive impairment. It is important to not exclude these patients from the study as it would significantly reduce our ability to produce generalizable knowledge.
The risks to subjects are minimal in relation to anticipated benefits and/or knowledge that might reasonably be expected from the results of this clinical trial. ICG is FDA approved for human use in angiography for ophthalmology and cardiology applications and is given routinely to patients in these clinical settings. The risks are considered minimal and consist of nausea, vomiting, hives, increased heart rate in subjects with particular sensitivity to the dye. ICG does contain sodium iodide and patients with a history of allergy to iodides will be excluded. The ICG will be administered thru IV which the patient will have regardless of if they participate in this trial or not. There will be no additional study specific IV's placed.

ICG, the Spy Elite® imaging system and the Zeiss Pentero 800 surgical microscope are FDA approved for use in human subjects. Currently we are enrolling patients into a study to evaluate the utility of first window ICG to identify areas of deficient perfusion. This study seeks to evaluate ICG utility as a second window in areas of deficient perfusion. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

Patients with impaired decision-making capacity will be included in this study. If the patient is unable to provide informed consent (e.g. due to their injury) at the time they are identified, informed consent may be obtained from their legally authorized representative (LAR). Allowing informed consent from a patient's LAR will reduce the risk of recruitment bias against the most severely infected patients.

For patient with impaired decision-making capacity, a LAR with knowledge of the potential participant will be approached to consent on the patient's behalf. If the patient cannot adequately answer at least two questions about the study or it is determined that the patient's level of cognition is not likely to change before study medication (ICG) can be administered, their LAR will be approached.. These questions will be to assess the participant's understanding of the study and what it means to participate, their appreciation of the consequences of participation, and their ability to consider alternatives to participation.

The choice of LAR will follow standard procedures. The following will be approached in this order of priority:

- Legal guardian
- proxy (health care agent) named in an advanced directive or durable power of attorney for health- care
- Family member or other surrogate identified by state law on health care decisions.

The LAR will be advised to base the decision on the participant's expressed wishes, or, if these are not known, what they believe the participant would have desired under the circumstances of the injury, their beliefs and values. Recognizing that consent is an ongoing process, the study team will encourage the participants to ask additional questions that may arise during the course of their participation in the study.

Subjects participation in this study completely voluntary. If at any time a patient finds participation to be unduly stressful the patient or their legal authorized representative may withdraw the patient from the study with no repercussions.

Assent will not be requested from subjects unable to consent for themselves.

The study team will comply with consent procedures for cognitively impaired adults outlined in SOP HRP-013.

This study will not recruit non-English speaking subjects.

This study will not involve the subjects who is under age 18.

No other vulnerable patient populations not outlined by this protocol will be included in this study.

22.0 Process to Document Consent in Writing

To obtain informed consent, study personnel will adhere to the following procedures: (1) present study information in a manner that is understandable to the patient; (2) discuss the study with the patient and answer any questions; (3) allow the patient an opportunity to discuss participation with their family; (4) confirm that the patient understands the risks and benefits of participating in the study and that their participation is voluntary; and (5) complete the consent process and obtain signatures from the patient and research team. The process of obtaining and documenting informed consent will be completed in accordance with Good Clinical Practice, outlined by the SOP HRP-090. The signed consent form will be uploaded to DHMC e-DH.

23.0 Setting

All consenting and imaging will be carried out in the orthopedic department, CRU clinic area or surgical unit at DHMC. All necessary patient follow-up with be conducted at the outpatient clinic. The data processing will be carried out by research staff within the administrative offices of the Orthopaedics Department located on level 5 of the Rubin building.

24.0 Resources Available

The Department of Orthopaedics at DHMC, a level 1 tertiary care academic medical center, has a robust research infrastructure. Research will be performed within the Orthopedic Surgery Department in the Rubin building, as well as in outpatient Orthopaedic clinics and CRU. All research personnel have been thoroughly trained and have been involved in multiple orthopaedic research studies. The Orthopaedic surgeons have weekly meetings to address any issues that arise during the process of care as well as any issues with ongoing research projects. While the medical and psychological risks from the study are minimal, and we do not anticipate any medical or psychological resources being needed for subjects enrolled in this study, should the need arise, subjects will be treated in accordance with usual standard of care for any medical or psychological issues, including but not limited to medical management, counselling, and appropriate consultation/referral.

All persons, including clinicians, faculty members, staff and students assisting with the research will receive instruction regarding the protocol, their duties and functions directly from the Principal Investigator. Additionally all research staff are trained before engaging in any activities in accordance with Dartmouth- Hitchcock policies for conducting research under Good Clinical Practices and have completed Collaborative Institutional Training Initiative (CITI) research ethics and compliance training.