PROTOCOL TITLE: Pilot feasibility study of dynamic contrast-enhanced fluorescence imaging to guide total shoulder arthroplasty approach

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Pilot feasibility study of dynamic contrast-enhanced fluorescence imaging to guide total shoulder arthroplasty approach

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

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VERSION NUMBER/DATE:

Version 1: 12/29/2021

PROTOCOL TITLE: Pilot feasibility study of dynamic contrast-enhanced fluorescence imaging to guide total shoulder arthroplasty approach

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?

Table of Contents

1.0 Study Summary

Study Title	Pilot feasibility study of dynamic contrast-enhanced fluorescence imaging to guide total shoulder arthroplasty approach
Study Design	Cross sectional study
Primary Objective	To evaluate the feasibility of open wide-field imaging of indocyanine green ingress and egress during total shoulder arthroplasty.
Secondary Objective(s)	To characterize the relationship between tissue perfusion measured with DCE-FI and different approaches and techniques used in total shoulder arthroplasty.
Research Intervention(s)/ Investigational Agent(s)	Assignment of research participants to subscapularis peel or tenotomy techniques utilized during total shoulder arthroplasty surgical approach. Indocyanine Green (ICG) indicated for soft-tissue perfusion assessment
IND/IDE #	N/A
Study Population	Patients who are undergoing open surgery for shoulder arthroplasty
Sample Size	10 patients
Study Duration for individual participants	4-6 weeks
Study Specific Abbreviations/ Definitions	AIF: arterial input function CDC: Centers for Disease Control and Prevention CRF: Case Report Forms DCE-FA: Dynamic Contrast Enhanced Fluorescence Arthroscopy DCE-FI: Dynamic Contrast Enhanced Fluorescence Imaging DoD: US Department of Defense D-HH: Dartmouth-Hitchcock Health DHMC: Dartmouth Hitchcock Medical Center FI: fluorescence imaging GCP: Good Clinical Practice GFR: glomerular filtration rate HRPP: Human Research Protection Program ICG: Indocyanine Green NSF: nephrogenic sclerosing fibrosis PDD: Pulse Dye Densitometer ROI: Region of interest SSI: Surgical Site Infection

PROTOCOL TITLE: Pilot feasibility study of dynamic contrast-enhanced fluorescence imaging to guide total shoulder arthroplasty approach

2.0 Objectives

The purpose of this pilot study is to evaluate the feasibility of open, wide-field imaging of indocyanine green ingress and egress during total shoulder arthroplasty.

The long-term goal of this work is to use DCE-FA for the assessment of subscapularis tendon perfusion and to determine potential relationships between perfusion and patient reported outcomes and subscapularis failure.

Primary Research Question:
To what degree does the relative perfusion of the subscapularis tendon—measured using DCE-FI—change after tenotomy vs peel technique and subsequent intra-operative repair?
Hypothesis: Perfusion of the subscapularis tendon will be reduced from baseline after tenotomy and peel techniques during shoulder arthroplasty.

Secondary Question:
Does DCE-FI with indocyanine green, used in a real time, intra-operative setting, highlight technique-dependent variations in subscapularis tendon perfusion during shoulder arthroplasty?

Aim: To determine if intra-operative ICG administration during shoulder arthroplasty can be coupled with an intra-operative surgical fluorescence detection device to determine alterations in subscapularis tendon perfusion before and after repair using peel and tenotomy takedown techniques for a deltopectoral approach.

3.0 Background*

Shoulder arthroplasty is a commonly utilized and routinely successful surgery performed for management of glenohumeral joint arthritis. Upwards of 90% of primary anatomic total shoulder arthroplasty surgeries are considered successful (Lapner *et al*., 2020). Albeit rare, complications do occur. Complications include glenoid or humeral component loosening, periprosthetic fracture, infection and rotator cuff failure. Of the four muscles that comprise the rotator cuff, the subscapularis is of particular concern in total shoulder arthroplasty surgery due to the approach used to access the glenohumeral joint. The deltopectoral approach is the standard approach used for shoulder arthroplasty and necessitates performing a subscapularis takedown in order to obtain adequate visualization of the glenohumeral joint. Three techniques to perform a subscapularis takedown are common, with an absence of consensus in the literature as to which technique is superior (Buckley *et al*., 2014). The techniques include a subscapularis peel, a subscapularis tenotomy and a lesser tuberosity osteotomy.

Each subscapularis takedown technique requires repair at the conclusion of the procedure when performing shoulder arthroplasty. Repair is crucial for proper force coupling of the shoulder to keep the humeral head implant centered on the glenoid component (Shields *et al*., 2017). Takedown is still performed in a reverse total shoulder arthroplasty but repair is not required to maintain stability. Each takedown technique is reliant on either tendon to tendon, tendon to bone, or bone to bone interface for healing. Failure of the subscapularis tendon repair can result in pain, instability, decreased functional outcomes and ultimately the need for revision surgery (Choate *et al*., 2018). Subscapularis tendon failure can sometimes be asymptomatic, however it can also be symptomatic and present with the aforementioned signs. Subscapularis failure rates may approach 50% in long term studies although symptomatic cases likely occur in less than 1% of total shoulder arthroplasties (Entezari *et al*., 2020). Due to the devastating impact on patients with symptomatic subscapularis failure, there is interest in investigating which subscapularis takedown technique produces the best outcomes. Prior randomized controlled trials as well as systematic reviews have previously been conducted looking at these different takedown techniques, but demonstrated no statistically significant difference in primary endpoints of subscapularis strength at various time endpoint and no statistically significant difference in patient reported outcomes (Lapner *et al*., 2020). These prior studies did not evaluate subscapularis perfusion post repair, adequate perfusion is necessary for healing to occur with any subscapularis takedown technique.

The takedown method of the subscapularis has previously been shown to have no statistically significant differences with regards to strength, or patient reported outcomes, however if there was a difference noted in tendon perfusion post repair this may provide rationale to choose one technique over another as improved perfusion may correlate to lower risk of repair failure. As this study aims to monitor subscapularis perfusion pre and post repair, the two techniques that the involve the tendon itself for healing will be utilized, peel and tenotomy.

The indocyanine green based DCE-FI will NOT be used to guide treatment or patient care. The data acquired using the SPY Elite or SPY PHI or EleVision will be anonymized and exported to a secure PC for additional analysis and processing. The analysis techniques will be more sophisticated than the current commercial system, and involve a correction for the patient-specific arterial input function (AIF) (Elliott *et al.*, 2020)—the cardiac and circulatory variations that can modify the time and manner in which the ICG dye arrives in the imaging field-of-view.

Indocyanine green (ICG) is a well-studied water soluble, light absorbing tracer that has been used in other capacities to help quantify tissue perfusion during

surgery. ICG is able to be injected into a patient intravenously and subsequently circulate systemically while bound to albumin, quickly undergoing hepatic metabolism in just several minutes (Faybik and Hetz, 2006). The concentration of ICG in specific tissue is able to be quantified as a surrogate for tissue perfusion. ICG due to its IV administration and quick metabolism is able to help quantify perfusion in real time, such as intra-operatively (Lutken *et al*., 2021). Systemic reviews as well as case studies, most commonly in plastic surgery, have been performed showing its utility to determine adequate or inadequate perfusion in downstream tissue in situations where microanastomoses are performed, such as with flaps (*Krishnan et* al., 2005) and in hand surgery (*Li et al., 2018)*. Other studies have also been conducted showing the ability to use ICG as a surrogate for tissue perfusion in the achilles paratenon in humans and in rabbits who had undergone rotator cuff repair to determine tissue perfusion after different types of repair. The use of ICG imaging in orthopaedic surgery is relatively nascent, and our institution (Gitajn *et al.*, 2020) as well as other collaborators (Sepehri *et al.*, 2021) have demonstrated its promise in these applications.

4.0 Study Endpoints*

Primary end point:

To assess the technology and its ability to see blood supply in the subscapularis tendon before takedown and after employed repair. The benchmark for this is the rise and fall of fluorescence signal approximately 10-40 seconds after injection. Given our experience in DCE-FI for bone fractures, it will be more or less self-evident whether the DCE-FA signal is sufficient for further analysis.

5.0 Study Intervention/Investigational Agent

5.1 Description:

This study is neither a drug nor a device trial. Patients will be administered FDA approved ICG through intravenous injection and imaged by a FDA approved surgical fluorescence imaging device (Spy Elite or SPY PHI or Medtronic EleVision) which is 0.5 meter away from the subject. Both ICG fluorescence and the imaging system 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 tendon perfusion can be captured by a video rate imaging system. The subscapularis takedown technique will alternate between tenotomy and peel for every other patient taken to the operating room. There is no reason intraoperatively to choose one technique over the other and therefore this puts

the patient at no added risk. If the surgeon feels that neither of these techniques are appropriate for the treatment of the patient then the patient will not be approached for enrollment.

5.2 Drug/Device Handling

Indocyanine green (ICG) used in this study will be ordered from the investigational pharmacy and supplied through the usual pharmacy dispensing mechanisms.

ICG is FDA approved for routine clinical practice in is currently available through the investigational pharmacy at DHMC. The results of this study are not intended to produce a new indication for the drug and will not be reported to the FDA. Nor will the results of this study significantly change the way that the drug is marketed in the United States. The medication will be utilized for an indication, and in a clinical setting, where it is currently utilized as part of usual care at this institution. ICG is lawfully marketed in the United States. The research will be conducted in compliance with the marketing limitations described in the FDA Code of Federal Regulations (21 CFR §312.7).ICG is FDA approved for routine clinical practice. No return or destruction of study drug is needed for this study.

The pulse dye densitometer (PDD) device used in this study is developed and tested by the Orthopaedics Translational Engineering Lab at DH. It is a modified pulse oximeter which is considered under the abbreviated IDE mechanism (see Section 6.2 for more information).

5.3 Dose Rationale

We plan a sample size of 10 patients in this open label prospective observational study of ICG fluorescence imaging for assessment of subscapularis tendon blood flow.

After the subscapularis tendon is visualized during the surgical approach, 0.1 mg/kg ICG will be injected intravenously. Video rate ICG fluorescence images will be acquired 20 seconds before and 4 minutes after ICG injection. This process will be repeated towards the end of the procedure after the subscapularis is repaired, but prior to skin closure.

This dose has been used to effectively assess bone perfusion in a previous study at our institution which was an IRB-approved pilot study. A total does of 0.2 mg/kg is within the range of previous studies. Indeed, this is 10 times less than the maximum recommended dose by FDA of 2 mg/kg.

6.0 Procedures Involved*

The research design for this study is a single cohort longitudinal study employing a consecutive sampling methodology. Eligible patients regardless of ethnicity or health

status, will be identified and recruited subject to inclusion and exclusion criteria listed in section 10. 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 legal authorized representative. 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.

Patients will be randomized to undergo either a subscapularis peel or subscapularis tenotomy.

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.

On the surgery day, 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 for arthroplasty of the involved shoulder joint.

A Pulse dye densometer (PDD; in-house developed), similar to a pulse oximetry probe, which is used clinically both in the operating room, in inpatients as well as outpatients to assess oxygen saturation. This is completely non-invasive. In the context of this study the pulse dye densometer collects data on the ICG injection parameters so that the kinetic curves can be normalized to injection-related differences. The PDD will be placed on the patient’s finger to acquire an arterial blood input function during ICG injection.

After the subscapularis tendon is visualized during the surgical approach, 0.1 mg/kg ICG will be injected intravenously. Video rate ICG fluorescence images will be acquired 20 seconds before and 4 minutes after ICG injection. This process will be repeated towards the end of the procedure after the subscapularis is repaired, but prior to skin closure.

ICG will be administered by an anesthetist in the operating room. Patients are under the care and observation of the anesthesia and surgical teams during this time. 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 30 minutes post-injection.

Day of surgery Procedures	Pre-Infusion	0-30 minutes post-infusion
Pulse	X	X
Blood Pressure	X	X
Temperature	X	X
Respiratory Rate	X	X
Adverse Events		X

Study patients will be seen per usual protocol for wound assessment and general health assessment after their shoulder arthroplasty at approximately 4 weeks post operatively.

6.2 Pulse Dye Densitometry Device

A Pulse dye densometer (Pulsion Medical Systems), similar to a pulse oximetry probe, which is used clinically both in the operating room, in inpatients as well as outpatients to assess oxygen saturation. This is completely non-invasive. In the context of this study the pulse dye densometer collects data on the ICG injection parameters so that the kinetic curves can be normalized to injection-related differences. We have a manuscript that was submitted for publication recently demonstrating the importance of collecting this data.

Data obtained as part of this study will not be submitted to or held for inspection by the FDA. The device is a custom device and is not being used to determine safety or effectiveness for commercial distribution.

Exemption Status: The device used is being evaluated on an observational basis. However, it is not exempt due to the fact it introduces energy into the subject. We request an abbreviated IDE under 21 CFR 812, given it is a non-significant risk device.

Description: The device comprises of a single Texas Instruments AFE4490SPO2EVM connected to (1) a Microsoft surface (Windows OS) and a (2) Nihon-KodhenTL-301P finger probe. The TI AFE4490SPO2EVM is an evaluation board with analog front-end that allows control and digitization of detected signal from a pulse oximeter. These devices come with a standard 660nm/900nm pulse oximeter finger probe, however, the Nihon-Kodhen probe (805nm/900nm) is used instead. A custom interface is built to

connect the NK probe (circular din connector) with the standard RS-232 connector on the TI board. The light produced by the NK probe is comparable to that of a pulse-oximeter and has a similar safety profile. The emission is well below the ANSI limits for skin exposure.

The IDE is not banned by the FDA, is labeled in accordance with FDA regulations and will not be marketed or promoted. The nature of the risk of the device is minimal. It does not present a potential for serious risk to the health, safety or welfare of the study subject. The device is not of substantial importance in diagnosing, curing, mitigating or treating disease.

7.0 Data and Specimen Banking*

Not applicable

8.0 Sharing of Results with Subjects*

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

9.0 Study Timelines*

All patients will participate in the following events shown in the table below. Follow up visits will be conducted during standard postoperative clinical visits or over the phone.

Assessment	**Visit 1:** Enrollment	**Visit 2:** Surgery	**Visit 3:** 1 month
Eligibility Screening	●		
Informed Consent	●		
Collection of Demographic & Shoulder Pathology Data	●		
Collection of Surgical Data (*e.g.* DCE-FI and AIF)		●	
Collection of Peri-Operative Data (*e.g.*, tHb and S_aO_2)		●	
Collection of Serious Adverse Events	●	●	●

We anticipate enrolling patients for 4-6 weeks for monitoring of serious adverse events. We anticipate completing preliminary analyses within about 6 months given the relatively small patient sample size and relatively high volume of total shoulder arthroplasty surgeries performed at Dartmouth-Hitchcock.

10.0 Inclusion and Exclusion Criteria*

PROTOCOL TITLE: Pilot feasibility study of dynamic contrast-enhanced fluorescence imaging to guide total shoulder arthroplasty approach

The clinical schedule of the orthopaedic surgeon who is the principal investigator will be reviewed by members of the research team for eligible study participants. Identified patients who meet inclusion criteria for the study will be provided information about the study by the orthopaedic surgeon, or a qualified member of their care team, at the time of their pre-operative clinic visit. Patients who wish to participate in the study will then undergo an informed consent process for the study.

Inclusion criteria:

a. Participant must be 18 years of age or older
b. Meet clinical and radiographic parameters necessary to undergo shoulder arthroplasty
c. Subscapularis tendon intact clinically on exam or via advanced imaging
d. Subject has the ability to have their shoulder arthroplasty completed using either the tenotomy or peel technique.

Exclusion criteria:

a. Inability of patient to provide informed consent
b. Iodine allergy
c. Subscapularis tendon tear or concern for tear
d. Incarceration
e. Pregnant women
f. Patients less than 18 years of age
g. Prior deltopectoral approach to the ipsilateral shoulder

11.0 Vulnerable Populations*

No Vulnerable patients will be enrolled in this study.

12.0 Local Number of Subjects

All 10 patients will be enrolled at this facility by the primary surgeon. This is a modest number of subjects to allow us to properly evaluate the feasibility of evaluating subscapularis tendon perfusion by two different takedown techniques in shoulder arthroplasty.

13.0 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.

Patients, 18 years of age or older who present to DHMC with shoulder arthritis who meet the inclusion criteria will be considered for enrollment. 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.

Upon identification, study personnel will screen the patient for eligibility and if eligible, the study will be introduced to the patient by a member of their care team. If the patient agrees, a member of the study team will approach them for informed consent. Screening will occur from the daily orthopaedic patient clinic schedule for the principle investigator. Study participants will be enrolled in the clinic setting prior to their surgical procedure.

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.

Potential recruits are instructed that their participation is completely voluntary and that their medical care will not be altered in any way should they elect not to participate at any time prior to surgery.

No advertisements or other promotional material will be used. No finder fees or recruitment incentives will be offered.

There will be no honorarium or payment in association with this study.

14.0 Withdrawal of Subjects*

Participants will be removed from the protocol if:

1) Concern for subscapularis tendon tear or insufficiency occurs.
2) The subject withdraws consent.

3) The subject has an occurrence of a significant clinical event that precludes proceeding with surgery.
4) Imaging cannot be completed for any reason

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.

For subjects who withdraw after the intraoperative imaging, but prior to their first post operative appointment, we will follow-up to see if they still complete their clinical follow up at the 1-month interval, and provide them an opportunity to report any adverse events. We will acquire their follow up results to include these subjects in the statistical analysis portion that only involves the intraoperative image data and infection status.

15.0 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 twice: once before and once after the repair. 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 urticarial 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, both surgical and anesthesia staff will monitor patients closely for any adverse reaction to ICG. Surgical and anesthesia staff will also monitor patients for at least 30 minutes after all ICG fluorescence assessment procedures have 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.

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: As with any protected health information, loss of privacy may lead to problems with insurability or social stigmatization. The risk to subjects is low and members of the research team will make every effort to ensure that information is kept private and protected to the fullest extent possible. Any and all information will be stored and managed in a secure manner, following all applicable federal regulations and guidelines and according to institutional policies and practices. Any electronic information collected will be stored on password protected, HIPAA compliant computers maintained in private, locked offices within secure areas of Dartmouth-Hitchcock Medical Center with limited access. Any non-electronic records collected will be stored likewise, as well. Any discussions between patients and the research staff will be conducted in a private location.

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.

16.0 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 subscapularis tendon perfusion and potential for correlation to outcomes.

17.0 Data Management* and Confidentiality

Data Confidentiality:

PROTOCOL TITLE: Pilot feasibility study of dynamic contrast-enhanced fluorescence imaging to guide total shoulder arthroplasty approach

The use of PHI is necessary for the purposes of this research and the PI and investigational team will protect the confidentiality of the subjects through the following actions:

Patients will be assigned a unique study identifier (*study ID*) based on the order in which they are recruited and a list of study IDs and the patients they correspond to (PHI) will be kept on a Dartmouth-Hitchcock secure server accessed by a DH laptop (the "H:/" drive). This is the only 'key' to matching patients and their corresponding study ID, and is only used to retrieve patient outcomes for the data analysis, and in the unlikely event that there is a reported adverse effect, to investigate the event.

A secured DH laptop will also store, in a separate document, a table containing the study date and anonymous study ID will be listed, along with any outcome information as it becomes available. This file will be kept separate from th*e file containing the study ID keys*, to minimize the chance it will be *inadvertently shared with* unauthorized individuals.

The file containing the study IDs and which patients they correspond to (ID Key), will be destroyed once all outcomes have been recorded and/or the follow-u*p period has passed, unless required* by the sponsor to maintain the information for an extended period of time. In that case, the ID Key will be destroyed at the earliest opportunity consistent with federal regulations.

Protected health information 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 research for which the use or disclosure of protected health information for which an authorization or opportunity to agree or object is not required by 45 CFR 164.512.

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

Since the PDD device does not meet the exempt criteria for an IDE, we request an abbreviated IDE determination from the IRB. Kevin McGuire, MD will serve as an independent research monitor for this study. He has expertise consonant with the nature of the risks identified within the research protocol and meets all of the following criteria:

a) Is independent of the team conducting the research involving human subjects.

b) Can stop the research, remove individual subjects, and take steps to protect subjects until the IRB assesses the monitor's report.

c) Will promptly report observations and findings to the IRB or other designated official.

d) Has an IRB approved written summary of duties, authorities, and responsibilities based on specific risks or concerns about the research.

e) Has confirmed in writing his/her duties, authorities, and responsibilities

With regards to patient safety, ICG will be administered by an anesthetist in the operating room while they are being continuously monitored per anesthesia standard of care. Post-operatively, they 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 30 minutes post-injection.

Day of surgery Procedures	Pre-Infusion	0-30 minutes post-infusion
Pulse	X	X
Blood Pressure	X	X
Temperature	X	X
Respiratory Rate	X	X
Adverse Events		X

With regards to data monitoring, the program manager at D-H will be responsible for ensuring that all patient data is complete. This will be monitored on a week-by-week basis and appropriate clinicians and/or research coordinators will be queried to complete incomplete patient data.

19.0 Provisions to Protect the Privacy Interests of Subjects

All identifying data will be kept in a restricted file on a secure DHMC server that can only be accessed by the PI and research coordinators. Participant data will also be entered in the "OnCore" database, which is a secure, password protected data collection system. Individual participants are assigned a random ID number within the OnCore database.

This database has restricted access, and the ability to view participant data is limited to specific members of the research team (e.g. PI and research coordinators).

No information will be disclosed to others without written permission from the patient, except:

- If necessary to protect the rights or welfare of the participant (for example, if the participant is injured and in need of emergency care); or
- If required by law.

Any discussion between the patient and the research staff will be conducted in a private location.

When the results of the research are published or discussed at conferences, no information will be included that would reveal participant identity. Authorized representatives of the D-HH IRB, Dartmouth College, and DHMC may need to review records of individual participants to ensure the accuracy of findings and to monitor the safety and welfare of study participants. The research imaging will not go into the patient's medical record and will not be used for any clinical decision-making.

20.0 Compensation for Research-Related Injury

This is an imaging study with minimal risk. We do not anticipate any injury or sickness happen due to the study. 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

21.0 Economic Burden to Subjects

There are no additional costs that subjects will accrue in association with participating in this research. 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 sponsor. They will not be billed to the patient.

22.0 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 recruit non-English speaking subjects.

This study will not involve any subject who is under age 18.

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

No cognitively impaired adults will be included in this study.

No other vulnerable patient populations will be included in this study.

23.0 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 EDH.

24.0 Setting

All consenting will be carried out in the outpatient clinic in the orthopedic department. Imaging for tendon perfusion will occur within the surgical suites 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.

25.0 Resources Available

The Department of Orthopaedics at DHMC, is a level 1 tertiary care academic medical center, and 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. 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.

26.0 Multi-Site Research*

Not applicable. We will only be enrolling patients from Dartmouth-Hitchcock.

27.0 References Cited

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