PROTOCOL TITLE: An Intraoperative Guidance Platform for Radio Frequency Ablation

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:

An Intraoperative Guidance Platform for Radio Frequency Ablation

PRINCIPAL INVESTIGATOR:

Eric Hoffer, MD
Department of Radiology
Section of Interventional Radiology
Dartmouth-Hitchcock Medical Center
One Medical Center Drive
Lebanon, NH 03756
Tel: 603-650-7417
Email: Eric.K.Hoffer@hitchcock.org

VERSION NUMBER/DATE: Version 1.1_10102019

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?

NCT: NCT04152343

PROTOCOL TITLE: An Intraoperative Guidance Platform for Radio Frequency Ablation

Table of Contents

PROTOCOL TITLE: An Intraoperative Guidance Platform for Radio Frequency Ablation

1 Study Summary

Study Title	An Intraoperative Guidance Platform for Radio Frequency Ablation
Study Design	Prospective, single center, single-arm clinical study
Primary Objective	To test the hypothesis that use of the research RFA Physics Library will result in more frequent technical success (complete necrotization of target tissues) compared to ablations conducted without computer guidance.
Secondary Objective(s)	To demonstrate that use of the RFA Physics Library will result in lower rates of local recurrence compared to ablations conducted without computer guidance.
Research Intervention(s)/ Investigational Agent(s)	The RFA Physics Library -- a Planning and Guidance Platform (PGP) (NE Scientific, LLC) -- will be used to support percutaneous liver RFA under CT-guidance by assisting physicians in the identification of ablation targets, assessment of proper ablation probe placement, and projection of the created ablation zones on the CT image.
IND/IDE #	TBD
Study Population	Adult patients with known hepatocellular carcinoma scheduled for percutaneous RFA.
Sample Size	52 patients
Study Duration for individual participants	One visit, during which the research PGP will be used to support physicians during the participant's scheduled standard of care RFA procedure. Use of the research PGP will not increase the time of the RFA procedure. Post-RFA, an abdominal MRI will be obtained for research purposes only. Duration of this MRI is approximately 30 minutes (including set-up and imaging). Participants will be followed for 2 years post-RFA for associated clinical outcome (local recurrence) information. .
Study Specific Abbreviations/ Definitions	Hepatocellular carcinoma (HCC) Interventional Radiology (IR) Operating Room (OR) Planning and Guidance Platform (PGP) Radio Frequency Ablation (RFA)

2 Objectives

Please reference SF19108 clinical protocol v29July2019, page 7, Section 2.0 Study Objectives

3 Background

Please reference SF19108 clinical protocol v29July2019, pages 4-7, Section 1.0 Introduction and Background

4 Study Endpoints

Please reference SF19108 clinical protocol v29July2019, pages 7-8, Section 3.1-3.2 Outcomes Assessments

5 Study Intervention/Investigational Device

5.1 Description of device

The investigational device used in this study is software called the RFA Physics Library--Planning and Guidance Platform (PGP), developed by NE Scientific LLC (Boston, MA) under the support of a SBIR Phase II grant (CA189515-03) awarded by the National Cancer Institute.

The investigational software is designed to support physicians during RFA treatment of HCC tumors (lesions), with the goal of improving the rate of complete ablation and thereby reducing the rate of local recurrence. Please reference SF19108 clinical protocol v29July2019, page 5, Section 1.2 Investigational Technology, for a high-level description of the PGP and its operation.

5.2 Abbreviated IDE information

We are requesting a Nonsignificant risk determination from the D-HH IRB.

The investigational device used in this study does not satisfy any of the criteria for a significant risk device:

a) It is not intended as an implant,
b) It is not for use in supporting or maintaining human life,
c) When used for supportive guidance in treating disease, it *does not* present a potential for serious risk to the health, safety, or welfare of a subject,
d) It does not otherwise present a potential for serious risk to the health, safety, or welfare of a subject.

Use of the investigational device in the context of this protocol has no potential for harm to subjects that could a) be life threatening, b) result in permanent impairment of a body function, c) result in permanent damage to body structure, or d) necessitate medical or surgical intervention to preclude permanent impairment of body function or permanent damage to body structure.

Use of the investigational device takes place at the same time as the subject's planned surgical procedure, which would occur independent of participation in this study. Use of the device during the procedure will not prolong or interfere with the planned surgical procedure.

The investigational device will be labeled in accordance with FDA regulations (21 CFR 812.5). Specifically, the investigational device (software) is installed on a laptop which is the property of NE Scientific LLC. The laptop will be in use at DHMC by the PI in full compliance with all institutional requirements for computer security and in full cooperation with D-H IT.

- The laptop will be labeled with the name and place of the manufacturer and the following statement: "CAUTION—Investigational device. Limited by Federal law to investigational use. Operation of this device is strictly limited to authorized personnel only."
- The operating system (Windows 10 Professional) on the laptop requires immediate log in (with password). No one without an account specific to that computer can access the PGP. Accounts are limited to the PI (Eric K. Hoffer, MD), the sponsor (Andrea Borsic, NE Scientific LLC), and D-H IT (for administrative purposes).
- A message box will pop up when the PGP application is started, and it will require the user to acknowledge the investigational use before the PGP software can be used.
- The PI will remove the laptop from the procedural suite immediately after each use. Outside of use during procedures, the laptop will be kept in the PI's locked office.

The investigator will comply with prohibitions against promotion and other practices as set forth in FDA regulations (21 CFR 812.7). Specifically, the investigator will not:

a) Promote or test market the investigational device until after the FDA has approved the device for commercial distribution.
b) Commercialize the investigational device.
c) Unduly prolong the research investigation.
d) Represent that the investigational device is safe or effective for the purposes for which it is being investigated.

6 Procedures Involved

Please reference SF19108 clinical protocol v29July2019, pages 9-13, Section 5.0 Study Procedures; pages 13-18, Section 6.0 Statistical Plan

7 Data and Specimen Banking

N/A

8 Sharing of Results with Subjects

Any new clinically significant findings from the study (post-RFA) abdominal MRI will be conveyed to the patient's primary (referring) physician.

9 Study Timelines

9.1 Duration of the individual subject participation

Study procedures occur during a single visit, during which the research PGP will be used in the standard of care RFA procedure. Use of the research PGP will not increase the time of the RFA procedure. Post-RFA procedure, an abdominal MRI will be obtained for research purposes only. Duration of this MRI is approximately 30 minutes (including set-up and imaging). Duration of follow-up for associated clinical outcomes (i.e. local recurrence) is 2 years post-RFA procedure.

9.2 Enrollment Duration

We expect to enroll 52 participants over 12 months.

9.3 Study Duration

Total study duration, from study initiation through patient enrollment and follow-up, is expected to be less than 4 years.

10 Inclusion and Exclusion Criteria

Please reference SF19108 clinical protocol v29July2019, page 9, Section 4.0 Subject Selection.

Patient eligibility for enrollment shall be based on known information at the time of the clinical RFA procedure. Information obtained at a later date may contradict these criteria, but this will not be considered a violation of the clinical protocol.

11 Vulnerable Populations

This study will not enroll members of vulnerable populations.

12 Local Number of Subjects

The study will enroll 52 participants.

13 Recruitment Methods

Participants will be recruited from the interventional radiology clinical practice. Patients scheduled for CT-guided RFA ablation of HCC lesions will be informed of the study and asked if they would like to participate. There will be no advertisements or other promotional material. There will be no finder's fees or incentives.

14 Withdrawal of Subjects

A participant may decide to withdraw from the study at any time without prejudice or loss of care.

The investigator may also decide to withdraw a participant from the study at any time based on medical judgement. A participant may be withdrawn from the research if:

a) Conditions change between consent and procedure such that the participant no longer meets the eligibility criteria, e.g. if the participant's HCC lesion is not identifiable on the procedural CT scan.
b) There are technical malfunctions during the study such that the data would not be analyzable, e.g., power loss, dysfunction of PGP software during the clinical RFA procedure.
c) The post-RFA abdominal MRI is not completed.

If a participant is withdrawn due to not completing the MRI portion of the study, or if the participant withdraws during the 2 year follow-up or is lost to follow-up, they will be included in the analysis of outcomes to the extent their data was been collected (e.g., if an MRI is missing, the imaging data may not be included in the technical success analysis, yet the participant may still be included in the clinical follow-up recurrence rate analysis.)

In the event that a participant revokes authorization to collect or use PHI, the investigator will retain the ability to use all information collected prior to the revocation of participant authorization. For participants who revoke authorization to collect or use PHI, the investigator will consult public records to establish survival status.

15 Risks to Subjects

Risks to participants as part of their involvement in this research protocol are minimal. A detailed statement of risks is described here:

Risks associated with use of the PGP

The following chart summarizes the differences between the standard clinical procedure (i.e. estimation of ablated tissues based on printed kill charts) and the PGP. Please reference Attachment A, "Risks and Safety Measures Associated with Use of the Research Software" for in-depth explanations.

Standard of care	Research PGP
Co-registration of Images Assessment of electrode position is based on intraoperative CT images capturing the deployed electrode. There is no co-registration to the contrast CT images highlighting the tumor.	**Co-registration of Images** The PGP software implements a rigid co-registration of the intraoperative CT images capturing the electrode to the contrast CT images highlighting the tumor.
Multiple Overlapping Ablations The interventionalist must build a mental map of which tissues have been treated and which still require ablation.	**Multiple Overlapping Ablations** The PGP software displays on the CT image which tissues have been treated by accumulating the volumes of each single ablation. Treated tissues and target tissues are shown in 2D and 3D.
Adequacy Assessment Ablation volume is estimated by mentally superimposing kill chart information to CT images. This requires mentally scaling, rotating and adjusting, and forming a 3D model of treated tissues and target tissues.	**Adequacy Assessment** The ablation volume is displayed superimposed on CT images in 2D and 3D, together with the tumor and margins. The overlap between treated and target tissues is evaluated visually in 2D and 3D views.

The physician can easily compare the visualizations of the manufacturer's kill chart and the PGP model by pressing the TAB key on the keyboard. (The PGP display clearly indicates which source of information is being used at the time.) The physician will assess the discrepancies (if any) between the kill chart and the PGP model predictions, and in all cases will perform the ablation procedure as is deemed to be safe and optimal for the patient.

- If the standard of care kill chart indicates specific tissues need to be treated and the PGP model indicates a smaller volume, the physician will defer to the standard of care kill chart tissue in order to minimize the risk of undertreatment. This is expected to be a rare occurrence.

- It is expected that the PGP model will frequently highlight additional tissue to be treated versus what is indicated by the manufacturer's kill charts alone. These will usually be small tissue volumes, e.g. an additional 2 - 3mm margin beyond kill chart estimates. In most cases, extending the ablation to this additional tissue is the very mechanism by which the treating physician can reduce the risk of recurrence. However, the physician will only proceed with ablation of these additional tissues (based on the research PGP estimates) if it does not pose a significant risk, i.e., the additional tissue is of negligible quantity with regard to liver function *and* the additional tissue is at least 1 cm from any critical structure.

- If the PGP model is within 1cm of vital structures, the physician will defer to standard clinical practice and proceed using the manufacturer's kill chart and standard clinical procedures.

- Overestimation, i.e. ablation of tissue in excess of what is needed to achieve adequate margins, is common in standard clinical procedures—because any given kill chart ablation zone rarely fits exactly to the desired target (tumor + margin), and so the surgeon routinely errs in favor of taking additional normal tissue rather than risk leaving tumor. We do not expect overestimation with PGP to happen with any greater frequency than in standard clinical procedures. It should also be noted that the alternative to RFA treatment of tumors, a surgical resection, routinely takes twice as much normal surrounding liver tissue—and this is a commonly accepted clinical practice.

Risks associated with the post-RFA abdominal MRI:
MRIs are part of the standard clinical work-up for HCC; approximately 90% of participants will have experienced an MRI exam prior to enrollment in this study. Some individuals may feel claustrophobic inside the MR unit. Potential participants are alerted to this possibility and will not be enrolled if known to be claustrophobic. Metal implants, such as surgical clips, and electronic devices, such as pacemakers, can be contraindications for MR exams. Participants are questioned about these conditions and enrolled accordingly. The post-RFA MRI will be performed using standard of care imaging units, and participants will be actively monitored, per clinical protocol, during the imaging session and following the completion of imaging.

Psychological risks:
Psychological risks are limited to possible transient distress related to discussion of the patient's cancer. The PI will be consenting patients and thus will be available to answer and attend to questions and anxieties concerning diagnosis. The Norris Cotton Cancer Center has clinical social workers on call if additional support is required.

Risk associated with loss of confidentiality:
Because clinical records (i.e. imaging exams) are viewed, the risk exists that the participant's medical records could be viewed by individuals who are not responsible for the participant's medical care or part of this research project. Individuals who are permitted to view participants' medical records may abuse the privilege and expose the patient to loss of confidentiality.

All participant data will be handled in a HIPAA-compliant manner which minimizes confidentiality exposure. Participants enrolled into this research study will be assigned study ID numbers and all data will be coded accordingly, with personal identifiers redacted or removed. Decoding information will be secured and accessible by a limited number of research personnel. All Dartmouth-Hitchcock research staff involved with this research project have completed the required IRB training regarding the protection of human subjects, and understand the importance of maintaining and protecting participant confidentiality.

16 Potential Benefits to Subjects*

Although the PGP model prediction is currently equivalent in accuracy to the manufacturer's kill charts, the PGP software provides the immediate advantage of clear visualization of either predicted ablation zone. Even experienced interventional physicians cannot accurately superimpose overlapping volumes when a larger tumor is treated with multiple ablations — and this is an essential function of the software. Participants should benefit from this advantage through better assurance of complete coverage of target tissues and minimization of non-target tissue damage. In turn, this should manifest as a decrease in local recurrence rates, possibly shorter procedure times, and fewer complications.

17 Data Management and Confidentiality

Please reference SF19108 clinical protocol v29July2019, pages 13-18, Section 6.0 Statistical Plan; pages 22-23, Section 8.0 Data Handling and Record Keeping

18 Provisions to Monitor the Data to Ensure the Safety of Subjects

Please reference SF19108 clinical protocol v29July2019, pages 18-22, Section 7.0 Safety and Adverse Events; pages 23-24 Section 9.0 Study Monitoring, Auditing, and Inspecting

19 Provisions to Protect the Privacy Interests of Subjects

All efforts will be made to protect the privacy interests of participants in this study and the personal health information collected as part of this study. Eligible participants will be at DHMC for a scheduled clinical procedure, and all DHMC staff are required to maintain and respect patient privacy in adherence to HIPAA and institutional regulations. Discussions about personal health matters and other personal information will be conducted in private areas, with patient access limited to required clinical staff.

20 Compensation for Research-Related Injury

This research is funded by NE Scientific, LLC through an SBIR Phase II grant (CA189515-03) awarded by the National Cancer Institute and compensation for a research-related injury or illness is not provided by federal law.

If participants are injured or become ill as a result of research procedures, they 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
- Norris Cotton Cancer Center
- Trustees of Dartmouth College
- NE Scientific, LLC
- National Cancer Institute

These organizations will not offer any payments for study-related illness or injury such as lost wages, expenses other than medical care, or pain and suffering.

If participants have any questions or concerns about the legal responsibilities of these organizations, they will be advised to call the Mary Hitchcock Memorial Hospital Office of Risk Management at (603) 650-1250 during normal business hours.

21 Economic Burden to Subjects

All procedures performed for research purposes will be paid for by the study. Participants and their insurance companies are responsible for all costs associated with standard clinical procedures.

22 Consent Process

The consent process will take place in the interventional radiology clinic office or in an interventional radiology pre-procedure area and will follow the D-HH IRB "SOP: Informed Consent Process for Research (HRP-090)".

Patients who meet the inclusion criteria and none of the exclusion criteria will be invited to participate in this study. During the patient's preoperative clinical visit (taking place 1-30 days before their ablation procedure), the PI will discuss the research protocol with eligible patients and will provide them with a copy of the IRB-approved consent form for their review. The PI is responsible for explaining the study (including risks), answering questions, and obtaining informed consent.

On the day of the scheduled procedure, the PI will again explain the study in detail and provide the patient with a new copy of the IRB-approved consent form to sign. The patient will then have the choice to enroll or not to enroll in this study. The patient will be provided with as much time as necessary to decide, and will have the option of speaking to family members or other associates if so desired.

Once informed consent has been obtained, the signed consent form will be scanned into the participant's medical record and a copy of the signed informed consent form will be given to the patient. The PI will document the patient's consent in the procedural note, located in the patient's electronic medical record.

23 Process to Document Consent in Writing

Each patient who agrees to participate will be required to sign an informed consent document prior to undergoing the clinical RFA procedure. We will follow the D-HH IRB "SOP: Written documentation of Consent (HRP-091)".

24 Setting

Research will be conducted in the Radiology areas of Dartmouth-Hitchcock Medical Center. Research procedures will be performed in the DHMC Interventional CT suites and MRI suites.

25 Resources Available

Approximately 100 cases of new or recurrent HCC are seen annually in the DHMC Liver Tumor Clinic. Based on recruitment efforts in the prior phase of this study (W17179), enrollment of >80% of those to whom it is offered may be expected. We believe it is reasonable to expect enrollment of 1-2 patients per week and to reach our target of 52 participants in 12 months.

The PI will initially devote 1 hour/week to conducting the research (i.e. enrolling patients and research procedures); this time will increase after the first few months to 2-3 hours/week to provide additional time for follow-up.

The available facilities include dedicated interventional radiology clinic space, two Philips interventional CT scanners, the Boston Scientific RFA Generator, and 4 permanent MRI scanners.

This research will be conducted in full cooperation with the DHMC Liver Tumor Clinic. If a participant requires counseling or support services, they will be referred to the clinical social workers program (in place at DHMC) for assistance.

The RFA procedure utilizes experienced, trained staff at all levels, as this procedure is standard of care. The data collection for the PGP software was tested in the protocol (W17179/CPHS#30520) for Aim 2 of the SBIR grant, thus the investigator and technologist staff are familiar with its use. All study procedures will be reviewed with the entire team during the 'time-out' that occurs before each case.

26 Multi-Site Research*

N/A