Study Title: Assessment of Sous Vide Water Baths in the Acute Rewarming of Frostbitten Extremities: A Multicenter Study Document

Date: 1/17/2023

NCT #: 05280301

PROTOCOL TITLE: Assessment of Sous Vide Water Baths for Acute Rewarming of Frostbitten Extremities.

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:

Assessment of Sous Vide Water Baths for Acute Rewarming of Frostbitten Extremities

PRINCIPAL INVESTIGATOR:

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VERSION NUMBER/DATE:

Version 2, 11/25/22

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1	11/25/2022	Addition of subject follow up and chart review at 6 months	Yes, reconsent required

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1.0 Study Summary

Study Title	Assessment of Sous Vide Water Baths for Acute Rewarming of Frostbitten Extremities
Study Design	Patients with acutely frostbitten hands or feet presenting to the emergency department will be consented to participate in the study. An ANOVA sous vide device will be attached to a water basin and set at 38°C. Two thermometers will continuously monitor water bath temperatures and the readings from the thermometers and sous vide device will be recorded every two minutes. The frostbitten extremity will remain in the circulating warm water bath for 30 minutes, at which time the extremity will be evaluated to see if rewarming is complete (warm to touch, pliable tissue). Tissue that is still frozen will be placed back into the water bath for an additional 30 minutes, at which time they will be reassessed. Medical providers directly involved in the care of the patient will fill out a survey regarding viability of this method and ease of use.
Primary Objective	To assess the ability of sous vide rewarming in maintaining constant water bath temperatures and efficacy in rewarming the acutely frostbitten extremity.
Secondary Objective(s)	To determine the ease of use of sous vide water bath rewarming in the acutely frostbitten extremity.
Research Intervention(s)/ Invest. Agent(s)	ANOVA Precision® Cooker sous vide device
IND/IDE #	NA
Study Population	Patients presenting to the emergency department with acute frostbite requiring rewarming; Providers to conduct rewarming, and complete a survey
Sample Size	1-5 patients locally, with anticipation of multicenter collaboration at 5-10 additional locations with similar enrollment goals.
Study Duration for individual participants	1-2 hours
Study Specific Abbreviations/ Definitions	SVD – sous vide device, SVR – sous vide rewarming

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2.0 Objectives*

- The purpose of the study will be to describe the use of a sous vide cooking device (SVD) in heating a water bath for the acute treatment of frostbite in the emergency department (ED).
- The aims will be to use this device in the treatment of an estimated 5-20 cases of acute frostbite in the ED, across a multicenter collaboration. The specific aims will be to assess the ability of the device to reach and maintain a target water temperature, and to survey those involved in the management of the patient regarding ease of use of this modality.
- Based on pilot study preliminary data, we hypothesize that the SVD will rapidly heat a small water bath, maintain the target temperature, and be considered easy to use.

3.0 Background*

- Frostbite is a clinical entity in which extremities, digits, and appendages undergo freezing damage due to exposure to environmental cold. Once in a safe environment where the potential for re-freezing is minimal, the current standard of care for acute frostbite is the rapid rewarming of the affected body part, using a circulating warm water bath targeted to 37-39^{o}C. There is no current "best" modality to warm and circulate the water. Depending on resources, this may be difficult and time consuming. In the field, water can be heated over a fire and added to a water bath. If heated water is present, hot tap water can be incrementally added to a water bath to achieve and maintain the targeted temperature. In the ED, some have advocated for placing the frostbitten hand or foot in a sink with running hot water and a thermometer in the sink to detect temperature. These methods are difficult at best, and may be dangerous in that they either do not maintain the water at the targeted temperature, or burn the frostbitten and often insensate extremity. An inexpensive, small, and transportable device that could reliably heat and circulate the water would decrease provider effort and optimize the water bath to the targeted temperature range. In remote locations where electricity is present but not reliably hot water, a portable heating device would drastically improve care.
- This modality is novel, and to our knowledge, has only been used clinically by our research group. In early 2020, a study was published investigating the in vitro use of SVDs in creating

circulating warm water baths for the rewarming of frozen pigs' feet. In this study, the SVD maintained the water bath at a constant 40ºC for 30 minutes and resulted in the rewarming of the pig foot from frozen to pliable. The sous vide modality was compared against and outperformed manual water exchanges. To test this clinically, we completed a pilot study in 2021 and successfully treated acute frostbite in the ED.

- Daniel NJ, Storn JM, Elder JH, Chevalier JI, Weinberg NE. Clinical Utilization of a Sous Vide Device in the Acute Rewarming of Frostbitten Extremities. *Am J Emerg Med.* 2021. DOI: https://doi.org/10.1016/j.ajem.2021.12.026
- Fiutko A, Foreman C, Mycyk M, Weber J. A novel approach to rapid rewarming of a frostbitten extremity: The sous vide method. Am J Emerg Med. 2020;38(3):463-465.
- This study will expand on the first documented use of sous vide rewarming (SVR) in the clinical setting and support proof of concept. Increased patient numbers will demonstrate the efficacy of using this method will provide the foundation for further study of SVR as a rapid, reliable, and portable modality for treating acute frostbite.

4.0 Study Endpoints*

- The primary study endpoint will be the rewarming of frostbitten extremities for 30 minutes at 38ºC.
- The secondary study endpoint will be a survey regarding ease of use of this rewarming modality.
- The primary safety endpoint will be patient pain or discomfort that is determined to be unrelated to the discomfort known to be associated with rewarming frostbitten tissue. Two consecutive temperature measurements above 42ºC will prompt the cessation of the SVR.

5.0 Study Intervention/Investigational Agent

1.1 Description: The intervention will be the use of a sous vide device to heat the water bath to 38ºC, rather than the traditional methods of manual water exchanges or placing the frostbitten tissue under running water.

- Drug/Device Handling: The SVD will be stored in a Tupperware container and appropriately labeled. The container will be stored in

a locked supply closet and only accessible by providers. This device is not used for other purposes in the ED, however signs on the container will read that this device is to be used only for this study.

- Cleaning the SVD:
  - A sign up chart will be taped to the container housing the SVD. The user will record the date of use, and upon returning the SVD to the container, will check a column indicating that they have sanitized the SVD with Purple SaniWipe cloths and a protocolized dishwasher detergent run.

6.0 Procedures Involved*

- Patients presenting to the ED at Dartmouth-Hitchcock and external study sites with acute frostbite (tissue still frozen) of the hands and/or feet will be identified and approached for recruitment. Patients not entering the study will continue to be treated by ED providers in the traditional fashion.
- Patients recruited for the SVR study will be consented to have their circulating warm water bath(s) heated by the novel SVR method. Providers or nurses caring for the study subjects will be consented to participate and will 1) conduct the SVR procedure, and 2) complete a questionnaire. A researcher will gather SVR equipment and attach two thermometers on the basin: one on the side nearest the SVD, the other on the opposite side. The researcher will verbally walk the provider or nurse carrying out the SVR through the following steps. A 15 L Sterilite® basin will be filled to the marked line (12cm) with water from jugs at room temperature, for each frozen extremity. One extremity can be rewarmed in a single basin, with the possibility for up to four simultaneous SVR basins for a patient with frostbite of all hands and feet. The SVD will be attached to the distal edge of the basin, with one SVD per rewarming basin. The SVD will be turned on and set to maintain the bath at a constant 38^{o}C for 30 minutes duration. The thermometers will be powered on continuously and the researcher will record temperatures simultaneously from each thermometer and the SVD every 2 minutes. At the end of the 30 minute treatment, the extremity will be assessed by the researcher for warmth and pliability. If the extremity still feels cold or frozen, an additional 30 minutes in the water bath will commence, with

subsequent reassessment. Rewarming will be considered complete when the affected tissue becomes red or purple, soft, and pliable.

- Patients who do not consent to SVR and elect for traditional water bath management will be asked for their consent to record the similar demographic, water temperature, and time-to-rewarm data as in the SVR treatment arm. After re-warming is complete, the provider will be asked to fill out a survey regarding the ease of use and efficacy of the SVR.
- *Describe:*
    - *Procedures performed to lessen the probability or magnitude of risks.*
        - Dual thermometers will record water bath temperature to assess for the possibility of disequilibrium in water temperature and to detect possible hot spots.
        - The treatment will be terminated if two consecutive thermometer recordings detect water temperatures of 42ºC or above.
        - The rewarming process in acute frostbite is inherently painful. Pain increases when water bath temps are above 40ºC. No additional discomfort is expected beyond that for frostbite rewarming, at the target temperature of 38ºC. The provider can provide analgesia as indicated. The treatment will be terminated if the patient has discomfort that is deemed by the treating provider to be above that expected from rewarming frozen tissue.
        - If treatment is discontinued prior to successful rewarming, standard rewarming will occur.
    - *Explain if any part of this study involves the use of procedures that are inconsistent with the standard of care at Dartmouth-Hitchcock Medical Center.*
        - There are no parts of the study that are inconsistent with the standard of care at DHMC. The novel treatment is to assess a treatment modality that may elevate the standard of care.
    - *All drugs and devices used in the research and the purpose of their use, and their regulatory approval status.*

- The ANOVA Precision® Cooker is a purpose-built device to maintain a set temperature circulating water bath. The device is not FDA approved for medical use. There will be no use of a placebo.
- The study treatment takes place entirely in the ED, which allows for comprehensive assessment of protocol compliance. If a subjects opts to discontinue participation at any time during the rewarming, standard techniques for maintaining the water bath will replace the SVD.

- *Describe randomization:*
  - All patients presenting with acutely frostbitten hands or feet will be approached for inclusion in the study. There is no randomization. Any patient not consenting to the use of the SVD but willing to allow data collection will act as a control group.
- *Prior and Concomitant Therapy:*
  - Concomitant therapies, such as intravenous fluids, anti-emetics, forced air warming blanket, and analgesia, as well as other medications deemed necessary by the provider, may be given concomitantly during the treatment period.
  - The blood pressure cuff used in the standard emergency department assessment of vital signs will be placed on an extremity that is not currently being rewarmed, whenever possible, to avoid constricting blood flow to the affected tissue.
- *Data Collection:*
  - Prior to rewarming, physical examination of the patient, including the frozen extremity, will be completed and documented in the EPIC/EMR chart by the provider.
  - Two thermometers, placed in the rewarming basin, will continuously monitor the water temperature. The temperature reading on both thermometers as well as the SVD will be recorded on a paper data sheet by a trained provider at 2-minute intervals until the 30 minutes of treatment are complete.

  - The researcher will repeat an exam, assessing all extremities being treated by SVR, at 30 minutes to determine warmth and pliability of the tissue, confirming thaw. Rewarming will be considered complete if the affected tissue becomes red or purple, soft, and pliable. The same rewarming criteria applies for all extremities.
  - The provider will be asked to fill out a survey on all acute frostbite patients whom consent to the study protocol, as well as those that do not.
- *The source records that will be used to collect data about subjects. (Attach all surveys, scripts, and data collection forms.)If there are plans for long-term follow-up (once all research related procedures are complete), what data will be collected during this period.*
  - The patient's age and sex will be recorded. The physical examination and pertinent medical information will be reviewed to confirm the location and extent of the frostbite and for contributing conditions.
  - Demographics and relevant medical history will be accessed.
  - Please see attached surveys and data collection forms.
  - Enrolled subjects may be contacted via phone and myDH or local electronic medical record communication at 6 months post-enrollment to assess long term outcomes of their frostbite. Chart review to assess related complications will also occur at this time.

- *Explain if any part of this study involves genetic analysis of biological specimens. If yes, explain whether the study is based on one the following:*
  - This study does not involve genetic analysis of biological specimens.

Provider Participation:

- *Role/Activities:*

  - Providers assigned to a patient in the emergency department who is determined to have acute frostbite will be targeted.
  - The provider's role will be to identify an acute frostbite patient and ask their patient whether they would be interested in hearing more about and potentially participating in a study assessing a new way to rewarm their frostbitten tissue.
  - If the patient agrees, the provider access the study on-call investigator list (posted in the ED provider area) and inform a researcher of the patient and need to discuss the stud and potentially enroll the patient.
- *Recruitment:*
  - Providers assigned to a patient in the emergency department who is determined to have acute frostbite.
- *Eligibility:*
  - Any provider managing a frostbite patient at the training levels of PA, APRN, resident physician, fellow, or attending physician are eligible.
- *Consent Process:*
  - One the patient has consented to participate, the provider will be consented in an area of the emergency department separate from the patient's room, using the provider consent form.
- *Risks/Benefits:*
  - Risks to providers should be minimal. We do not anticipate providers having any difficulty with voluntary decision-making for this study.
  - Benefits to the provider may include improved work flow due to the decreased labor in maintaining a SVR water bath in comparison to manual water bath management. Additionally, participation will provide a firsthand opportunity to treat acute frostbite with a new modality that has potential for increased use in the future.
- *Data Collection:*
  - After successful completion of the SVR, providers will be asked to take a short, 6-question paper survey regarding ease-of-use of the SVR.

- Paper data collection forms will be kept in a locked office until transferred by the PI to a Microsoft excel file on a password-protected DH computer.

7.0 Data and Specimen Banking*

- There will be no specimens banked for future use.
- Individual patient data from the emergency department visit will exist in the patient's EMR.
- A de-identified, numerically listed spreadsheet of the study participants will be stored on the protected Dartmouth-Hitchcock H: drive of the PI. The participant key will exist on the same drive. The PI computer is a D-H managed ThinkPad and will remain on-campus in a locked office shared by the PI.
- Consented subjects will be tracked in the DHH CTMS, OnCore

8.0 Sharing of Results with Subjects*

- Neither the individual subject or study results will be shared directly with the subjects or others, including the subject's primary physician. The study results will be shared via publication.

9.0 Study Timelines*

- *Describe:*
  - Each participant will be enrolled during the study period for this treatment, which includes the emergency department visit. The actual estimated treatment duration is 30 minutes. Some participants may exceed this and be treated for 60-90 minutes.
  - Given the incidence of frostbite and census of the Dartmouth-Hitchcock emergency department, and the requirement for the participant to have acute frostbite (currently frozen) rather than already thawed, it is expected to take the entire cold frostbite season to enroll 1-5 participants per study enrollment location.
  - The estimated date for the investigators to complete this study: Sept 11, 2023.

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10.0 Inclusion and Exclusion Criteria*

- The primary and sub-investigators will identify patients presenting to the emergency department with a chief complaint of frostbite, as seen on the EMR patient tracking board. Reminder signs and group awareness in the emergency department of this study will help alert providers of the potential to approach subjects for enrollment who presented to the department with an associated complaint, such as "foot pain" or other chief complaint, but determined to have acute frostbite on initial examination. The PI or a Sub-I will be on-call to drive to the ED to enroll and consent the patient with the standard forms, and assist with the treatment. Consent will always be obtained in-person, by a study team member with consenting privileges. *Inclusion criteria:* Age 18 or up or <17 with parent or guardian able to provide consent, ability to understand English and provide consent to the study, acute frostbite (frozen tissue) of the hands or feet.
- *Exclusion criteria:* Children under age 18 without parent or guardian, frostbite that has already thawed, frostbite (thawed or acute) of tissue other than hands or feet, inability to understand English and to provide consent.
- *Indicate specifically whether you will include or exclude each of the following special populations: (You may not include members of the above populations as subjects in your research unless you indicate this in your inclusion criteria.)*
    - *Adults unable to consent* - Exclude
    - *Individuals who are not yet adults (infants, children, teenagers)* - Include
    - *Pregnant women* - Include
- *Prisoners* - Exclude

11.0 Vulnerable Populations*

- This study presents no more than minimal risk to enrollees. There is no expected increase in risk to children or pregnant women over standard care treatment options. Excluding these populations may limit the sample size of the study.

12.0 Local Number of Subjects

- The maximum available to enroll will be enrolled during the study period. The investigators estimate 1-5 patients per study location may be feasible during the cold season.

Describe the statistical methods for determining the sample size for the study

- N/A. As a feasibility study to the use of SVR for acute frostbite, there are no sample size calculations. All potential participants will be approached for enrollment.

13.0 Recruitment Methods

- Patients presenting with acute frostbite in the Dartmouth-Hitchcock Emergency Department and participating centers and whom have expressed interest in participating in the study to their care team will be approached for recruitment during their emergency department visit.
- Patients will be identified by the PI, Sub-Is, and other providers by the chief complaint, which may state frostbite, cold-injury, or pain in an extremity. Word-of-mouth and departmental awareness of this study will assist providers in identifying the appropriateness of recruiting patients that had varying other chief complaints, but found to have acute frostbite on evaluation.
- Subjects will be recruited in person, during their emergency department visit and will be consented by the research team.
- There will be no payments for participation in this study.
- Some participating sites will request a Partial HIPAA Waiver of Authorization for Recruitment Purposes so that the research team can scan the emergency department electronic medical records board for patients presenting with frostbite. It is critical that the SVR is implemented quickly, which allows for the best treatment efficacy. By scanning the emergency department board, the research staff will more rapidly identify frostbite patients and circumvent possible delays in enrollment and treatment.

14.0 Withdrawal of Subjects*

- Subjects will be withdrawn without their consent for safety reasons or medical necessity. Criteria as follows: If water bath temperatures are recorded at over 42ºC on two consecutive readings during the

same treatment phase, if subject is judged by the treating clinician to have pain greater than expected for frostbite rewarming, or if a separate medical issue arises in the subject in which urgent treatment necessitates termination of the research.

- *Describe any procedures for orderly termination.*
    - The SVD will be powered off and the water bath maintained manually by medical staff.
- *Describe procedures that will be followed when subjects withdraw from the research, including partial withdrawal from procedures with continued data collection.*
    - Withdrawal from the research will preclude any further data collection. Data already collected at the time of the withdrawal will be analyzed with other study data but noted that the study terminated prematurely.

15.0 Risks to Subjects*

- *List the reasonably foreseeable risks, discomforts, hazards, or inconveniences to the subjects related the subjects' participation in the research. Include as may be useful for the IRB's consideration, a description of the probability, magnitude, duration, and reversibility of the risks. Consider physical, psychological, social, legal, and economic risks.*
    - The standard of care for acute frostbite rewarming, which is a circulating warm water bath, will not be altered and patients will receive the standard of care treatment. The only alteration is the method of maintaining the warm water bath. Frostbite rewarming is known to be a painful process. Pain control will be at the discretion of the treating physician and the study will have no implications on this aspect of care.
    - Potential hazards include hot water burns and the unlikely chance of catastrophic device failure and electrical injury. There were no adverse events reported during the pilot study. Hot water burns are also a risk in the current practice of manual hot water bath management, and the SVD may actually mitigate this risk by improved temperature control. Biomedical engineering at Dartmouth-Hitchcock has assessed the ANOVA SVD.

- The investigators do not see any specific psychological, social, or economic risks to the subjects directly related to the research, as the circulating water bath rewarming method is the standard of care for frostbite management.

If applicable, explain how the use of the placebo or non-standard of care therapy may affect risks for participants, addressing the following:

- *The safety and efficacy of other available therapies*
  - The current available therapy for frostbite rewarming is the same as being used in this study – circulating warm water bath. The study will use a new technique to creating this water bath. SVR is expected to be more efficacious than the current method of water bath management.
- *The greatest potential harm that may result from not receiving or delaying effective therapy*
  - While unlikely, it is possible that the SVR would not heat the water and delay time to the current practice of manual water bath management. If this were to occur, delay to therapy would be minimal as the only change in intervention would be the manual addition of warm water to the basin. It is expected that the research treatment will speed up the delivery of effective therapy.
  - Risk will be minimized by assessing the water temperature continuously. The SVR will be ceased and the manual rewarming started if the water bath does not reach the target temperature in 30 minutes, or if the water bath temperature drops below 37ºC for more than 5 minutes.
  - If providers are unable to reach an on-call investigator and determine their availability within 20 minutes from the patient expressing interest in the study, standard rewarming will proceed via traditional water exchange practices.

- *If applicable, indicate which procedures may have risks to the subjects that are currently unforeseeable.*

  - Unforeseeable risks different than typical water bath rewarming, if any, would relate to SVD failure. To further minimize this unlikely event the SVD will be physically checked for any signs of wear following each utilization at

the time of cleaning. The SVD has been assessed by biomedical engineering at Dartmouth-Hitchcock and deemed low risk.

16.0 Potential Benefits to Subjects*

- *Describe the potential benefits that individual subjects may experience from taking part in the research. Include as may be useful for the IRB's consideration, the probability, magnitude, and duration of the potential benefits.*

    - The current method of creating and maintaining a circulating warm water bath is arduous, time consuming, and not controlled. It is highly suspected that the research method of water bath management will be quicker to achieve target water temperatures, safer in that the water temperature will be electronically monitored and maintained, and will benefit the patient in the expedited thawing of the frozen tissue.

17.0 Data Management* and Confidentiality

- *Describe the data analysis plan, including any statistical procedures or power analysis.*

    - The primary outcomes are whether or not the tissue rewarmed and the ability of the SVD to maintain accurate target water temperature. Descriptive statistics will be performed to describe the patient population, time to rewarm, and the provider assessment of ease of use.

- *Describe the steps that will be taken to secure the data (e.g., training, authorization of access, password protection, encryption, physical controls, certificates of confidentiality, and separation of identifiers and data) during storage, use, and transmission.*

    - Paper data collection forms will be kept in a locked office until transferred by the PI to a Microsoft excel file on a password-protected computer. The identifiers and data will be contained in two separate files. Only the PI and sub-investigators will have access to the de-identified data and the PI will retain sole access to the identification key.

    - Data from other sites will be uploaded directly into REDCap database hosted by DHMC to ensure secure data transfer for multicenter analysis. Access to the data on the

REDCap database will be restricted to the PI and DHMC study staff.

- *Summarize the record retention plan applicable to the study (taking into account any applicable Dartmouth Department, Division or Research Center requirements, or applicable funding sponsor requirements.)*
    - Records will be stored on-site on the PI's password protected computer for 3 years after publication.
- *Describe any procedures that will be used for quality control of collected data.*
    - Dual thermometers will act as redundant sampling of water bath temperatures
- *Describe how data or specimens will be handled study-wide:*
    - *What information will be included in that data or associated with the specimens?*
        - The data collection form will include the MRN of the patient and a numeral used to de-identify the data in the excel file. The collection form will contain a table of recorded water temperatures, including a temperature from each of the two thermometers as well as the SVD every 2 minutes during the rewarming period. Any adverse events will also be recorded.
    - *Where and how data or specimens will be stored?*
        - Data collection forms filled out by clinicians or investigators will be stored in a locked office until the data is transferred to a Microsoft excel file. The data file will be stored on the password-protected computer of the PI.
    - *How long the data or specimens will be stored?*
        - Data will be stored throughout the duration of the study and manuscript preparation.
    - *Who will have access to the data or specimens?*
        - The data collection forms will be accessible to the clinician filling it out. Once transferred to excel format, only the PI and sub-investigators will have access to the de-identified data. Only the PI and key study personnel will have access to the de-identification number key.

- *Who is responsible for receipt or transmission of the data or specimens?*
    - Data collection forms will be deposited in the locked office by the clinician or investigator filling out the form during active rewarming of a subject.
    - Data will be entered into REDCap for further analysis.
    - External sites will enter their data directly into the DH REDCap Database
- *How data or specimens will be transported?*
    - Data will remain on the password protected hard drive of the PI.
    - Deidentified data may be analyzed by additional research team members.

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

- *Describe:*
    - *The plan to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe. The plan might include establishing a data monitoring committee and a plan for reporting data monitoring committee findings to the IRB and the sponsor.*
        - The data will be reviewed by the local PI each time a subject participates in the study, to confirm standard process and to assess for reported adverse events.
        - As the lead site, we will review all data entered into the database for completeness.
    - *What data are reviewed, including safety data, untoward events, and efficacy data.*
        - Signed informed consent, temperature recordings, water bath treatment time required to achieve rewarming, and adverse events will be reviewed.
    - *How the safety information will be collected (e.g., with case report forms, at study visits, by telephone calls with participants).*
        - Adverse events will be recorded on the data collection form during the treatment of the subject in the emergency department.

- Adverse events across all sites will be reviewed at a monthly meeting of collaborating sites.

- *The frequency of data collection, including when safety data collection starts.*
  - Data collection will commence when the subject is treated in the emergency department. Data will be reviewed for safety issues after each subject.
- *Who will review the data.*
  - The PI will review the safety data.
- *The frequency or periodicity of review of cumulative data.*
  - The PI will review cumulative data after each subject.
- *The statistical tests for analyzing the safety data to determine whether harm is occurring.*
  - With an expected subject size of 1-5 study participants in each study location, safety data will be reviewed after each subject participates. There will be no need to make estimations.
- *Any conditions that trigger an immediate suspension of the research.*
  - If 1 or more unanticipated adverse events are considered possibly attributable to the use of the SVD, the study will be put on hold pending review of the incident.
- *Describe the procedures for unblinding study therapy on a subject, including documentation of this in the subject's source document.*
  - Unblinding study therapy will not be necessary, as the study is unblinded to the participant and the clinician treating the subject and the treatment will occur only during the rewarming phase in emergency department visit.

19.0 Provisions to Protect the Privacy Interests of Subjects

- *Describe the steps that will be taken to protect subjects' privacy interests. "Privacy interest" refers to a person's desire to place limits on whom they interact or whom they provide personal information.*

- Patients who may meet the enrollment criteria will be approached and asked if they are willing to learn about a research study taking place that they may qualify for. If the patient is not interested they will receive the current standard of care treatment.

- *Describe what steps you will take to make the subjects feel at ease with the research situation in terms of the questions being asked and the procedures being performed. "At ease" does not refer to physical discomfort, but the sense of intrusiveness a subject might experience in response to questions, examinations, and procedures.*

    - Potential subjects will have the traditional method of rewarming explained as well as an explanation of how SVR works. They will be informed that research is voluntary and they can withdraw at any point.

- *Indicate how the research team is permitted to access any sources of information about the subjects.*

    - The study team will be permitted to access the emergency department chart of the consented subjects to be able to record de-identified sex, age, frostbite location, further information about the case or any adverse event, and patient outcomes. The subject provides consent for this access as part of the informed consent process.

20.0 Economic Burden to Subjects

- *Describe any costs that subjects may be responsible for because of participation in the research.*

    - Hot water burns or electrical failure causing injury and the treatment of such injuries would be the only foreseeable costs incurred by the patient. The burn risk is present in the traditional method of frostbite rewarming and the SVR is expected to minimize this risk. Biomedical engineering at Dartmouth-Hitchcock has assessed the SVD, deemed it low risk, and cleared it for use.

21.0 Consent Process

- *Indicate whether you will you be obtaining consent, and if so describe:*

    - *Where will the consent process take place*

  - Patient interest in study participation will be determined in the emergency department exam rooms (not the waiting room) by the provider. Patient consent will then be obtained in emergency department exam room by the investigator.
  - Upon patient consent, the researcher will approach the provider to obtain consent. Provider consent will occur in the participating emergency departments in a separate location outside of the patient's exam room. The SVR will not proceed without patient consent, therefore, provider consent will be obtained only once patient consent has been obtained.
- *Any waiting period available between informing the prospective subject and obtaining the consent.*
  - None. The prospective subject will be identified and consented at the earliest convenience as to avoid delaying emergency department rewarming. If providers are unable to reach an on-call investigator and determine their availability within 20 minutes from the patient expressing interest in the study, standard rewarming will proceed via traditional water exchange practices.
- *Any process to ensure ongoing consent.*
  - Upon initial consent, the subject will be informed that they are able to withdraw from the study at any point during the rewarming period.
- *Whether you will be following "SOP: Informed Consent Process for Research (HRP-090)." If not, describe:*
  - SOP: Informed Consent Process for Research (HRP-090) will be followed.

Non-English Speaking Subjects

- Inability to understand and speak English are exclusion criteria for this study.

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

- *Describe the criteria that will be used to determine whether a prospective subject has not attained the legal age for consent*

to treatments or procedures involved in the research under the applicable law of the jurisdiction in which the research will be conducted. (E.g., individuals under the age of 18 years.)

- *Describe whether parental permission will be obtained from:*
  - *One parent even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child.*
    a. All subjects age 18 and overall will be asked to provide informed consent.
    b. All subjects ages 7-17 will be asked to provide assent in addition to consent of one parent or legal guardian.
- All subjects ages 2-6 will be enrolled if consent of one parent or legal guardian is provided. *Describe whether permission will be obtained from individuals other than parents, and if so, who will be allowed to provide permission. Describe the process used to determine these individuals' authority to consent to each child's general medical care.*
  - If a parent or legal guardian is not present to provide consent, patients under age 18 will be excluded.
- *Indicate whether assent will be obtained from all, some, or none of the children. If assent will be obtained from some children, indicate which children will be required to assent.*
  - Subjects age 7-17 will be asked to provide assent.
  - A prepared assent form using more simple language, but mirroring the adult consent, will be used as the basis to provide information to the subject aged 7-17 and for the assent process.
  - Subjects under age 7 will not be asked to provide assent.
- *When assent of children is obtained describe whether and how it will be documented.*
  - Confirmation off assent will be recorded in the appropriate location on form HRP-502 and comply with SOP HRP-091

22.0 Process to Document Consent in Writing

This study will comply with SOP: Written Documentation of Consent (HRP-091) when the patient is physically able to sign the consent documentation.

PROTOCOL TITLE: Assessment of Sous Vide Water Baths for Acute Rewarming of Frostbitten Extremities.

We are requesting an alteration on the documentation of informed consent for subjects who are physically unable to sign. The consent process will remain unchanged from section 21.0 of this document, however given the enrolling population it is feasible if not expected that some potential subjects will present with bilateral frostbite of the hands and be physically unable to sign for themselves.

In cases where the patient is unable to legibly initial, sign and date, due to injury to the hands, but is able to make a mark on the page, the patient will make a mark on/near the line for initials and the place for signature. A witness who is an impartial third party will observe consent discussion and the marking of the consent. The witness will acknowledge that they saw the subject make his mark on the specific date and then sign, print name, and date the witness section of the consent form.

In instances where the patient is unable to make any mark on the consent form we will obtain and document verbal consent from the patient on the consent form and have an impartial third party serve as witness to the consent process. The person obtaining consent will sign and date the consent form. The witness will acknowledge that the informed consent was fully explained and the subject understood the study details. The witness will sign, print name, and date the witness section of the consent form.

Only one consent form will be used for up to four extremities being treated for frostbite using the SVR rewarming process detailed in this document.

23.0 Setting

- *Describe the sites or locations where your research team will conduct the research.*
    - The research team will identify, recruit, and perform the study treatment in the Dartmouth-Hitchcock emergency department, which is a Level I Trauma center. The other study sites include the emergency departments at: TBD. All are Level I trauma centers, except for TBD, which is TBD.

PROTOCOL TITLE: Assessment of Sous Vide Water Baths for Acute Rewarming of Frostbitten Extremities.

24.0 Resources Available

- This research study has the support of the emergency department chair. As PI, Dr. Daniel will dedicate as much time as necessary to oversee and ensure appropriate conduct of this study.
- We are working with our Director of Research Operations to ensure compliance with institutional practice and appropriate regulatory management.
- The Dartmouth-Hitchcock Emergency Department is an academic, level I Trauma center with an annual patient volume of approximately 35,000. The patient volume of other participating centers range from TBD to TBD.
- The human research component is comprised of 30-90 minutes of treatment by placing hands and/or feet in a warm water bath. As such, there is unlikely to be untoward medical or psychological consequences. Should medical or psychological consequences occur, the study is being completed in a Level I Trauma center emergency department that contains the resources to address any unforeseen issues.
- All persons assisting with the research will undergo one-on-one training with the PI regarding the recruitment plan, consent process, and research procedures including monitoring, managing, and recording data on the participant and water bath, as well as protocols for cleaning and storing the SVD. A comprehensive email containing this information will be sent to all persons assisting as a reference.