Socket Cooling Effectiveness Study

Investigators	Todd Farrell, PhD **Liberating Technologies, Inc.** 325 Hopping Brook Road, Suite A Holliston, MA 01746 (508) 893-6363 John Ferguson, PhD **Minneapolis VA Health Care System** One Veterans Drive Minneapolis, MN 55417 (612) 629-7471 Gordon Hirschman **Vivonics, Inc.** 175 Great Road, Ste 110 Bedford, MA 01730
Sponsor	Department of Defense – Joint Warfighters Medical Research Program
Sponsor Protocol #	
NEIRB #	120180039

1. Background and Introduction

The comfort and fit of the residual limb within a prosthetic socket are of primary concern for many amputees. The residual limb is typically covered by non-breathable and non- thermally conductive materials that can create a warm and ultimately moist environment. Studies found increases in socket temperature after the prosthesis was donned (0.8°C) [Peery 2005] and after 30 minutes of walking (2.5°C) [Huff 2008]. Temperatures were found to remain elevated long after activity cessation and even a rest period of double the duration of the preceding activity period is insufficient to return the limb to its initial temperature [Klute 2007]. Peery, et al. suggested that a modest temperature increase of only 2°C may be responsible for reports of thermal discomfort by amputees [Peery 2005]. Therefore, a small amount of activity can cause the socket temperature to elevate and remain at an uncomfortable level for an extended period of time, which can lead to decreased wear times. In summary, an uncomfortable socket/residual limb interface decreases prosthesis use among amputees who want to remain active in their lives.

To address this, Liberating Technologies, Inc. (LTI) and Vivonics, Inc. have developed a thermo-electric cooling (TEC)-based module called the Intrasocket Cooling Element (ICE), that can be embedded into the prosthesis in order to cool the residual limb. A technology that can provide thermal control while retaining adequate suspension, weight and other prosthetic characteristics would benefit many prosthesis wearers.

2. Study Rationale

This study will focus on investigating the efficacy of this novel socket cooling technology.

The rationale for this study is to determine how well the new technology can cool the residual limb not only in a controlled laboratory environment, but also in a home environment where the device would ultimately be utilized.

3. Objectives

The primary objective of this study is to measure the effects of cooling the residual limb on quality of life (QoL) and functional outcomes. Cooling the residual limb inside the prosthetic socket would result in less sweating and greater comfort while wearing the prosthesis, and ultimately greater function and better quality of life as measured by standard functional and QoL outcome measures.

4. Study Design

A two group, prospective, double-blinded, block randomized, crossover study design will be implemented. Research participants will be consented and have baseline activity and socket temperature data collected from their usual prosthesis during normal use (4 weeks). The ICE system will be integrated into a custom, experimental socket for each subject. Two versions of the cooling module will be created: (1) a fully-functional, active ICE cooling module (the so called “ON”, or experimental, condition), and (2) a placebo ICE module with the TEC unit replaced with an insulating material layer between the fan and the heat spreader such that even when the system is turned on, minimal heat transfer occurs (the control, or “OFF” condition). An ICE module with a heat spreader will be embedded into the socket and the fan will continue to run whether or not active cooling is engaged for both test conditions; however, no heat will be able to be transferred through the insulating layer in the OFF condition. The TEC inside the ICE unit will not be visible once assembled

and the modules will be assembled independently; therefore, both the subject and the tester will be blinded to the condition being tested for both the in-lab and at-home testing. A serial number will be used to identify the assembled units and the master key stored separately.

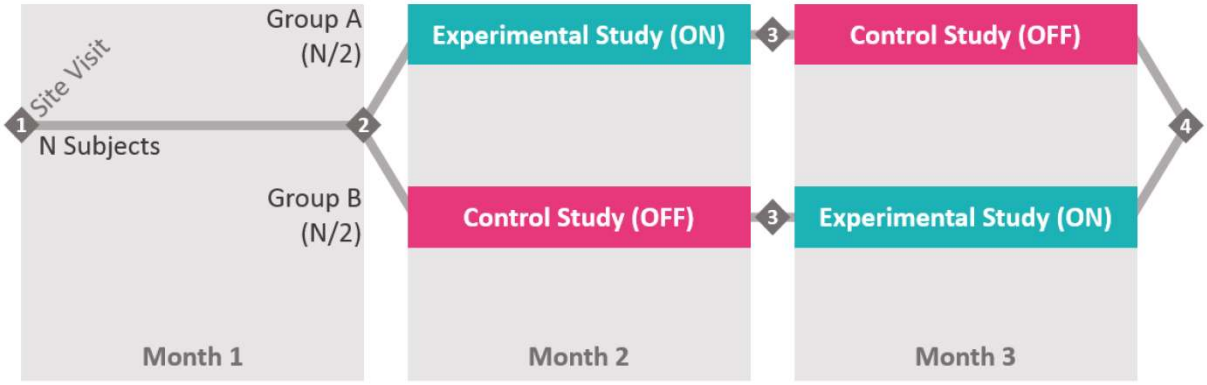

Figure 1 | Timeline of human subjects testing.

The participants will be divided into two groups and the order of the experimental conditions will be randomized. Each condition will be tested for 4 weeks. In-lab testing and functional measures will be assessed between testing periods as additional assessments of efficacy of the device. Testing will consist of 4 test site visits, as well as 1-2 visits to create and align the experimental socket. The entire study will continue for 3 months.

5. Study Population

Lower limb prosthesis users will be recruited for the study and consented with an approved protocol. Research participants will represent a convenience sample and will reflect the local population of both above-knee (AK) and below-knee (BK) amputees of various K-levels using a variety of suspension types who could benefit from temperature control within the socket.

A power analysis revealed that 8 subjects would be required to determine whether our device can provide clinically significant cooling to the residual limb in a prosthetic socket. While the recruitment of anything above a modest number of amputees can be challenging, we have mitigated this challenge by partnering with the Minneapolis Veteran Affairs Health Care System (MVAHCS) so that testing will occur at both LTI in Holliston, MA and at the VA in Minneapolis, MN, to increase our pool of potential subjects from multiple geographic areas and to require multiple prosthetists to integrate the ICE system into the test sockets. LTI will enlist the aid of its current in-house prosthetist, Michael Amrich, CPO and its network of prosthetists including Next Step B&P, Cornell O&P, and several others, to assist in subject recruitment. In Minneapolis, subjects will be recruited from the Minneapolis VA Regional Amputation Center database, which includes over 840 patients with amputations who have received medical care over the last decade. This database is currently being used for screening potential research participants for multiple ongoing studies at the Minneapolis VA, with approval from the Minneapolis VA's Institutional Review Board. The majority of the patients in the database have lower-limb amputations. Because we are performing testing at two different test sites (LTI and MVAHCS), to be conservative, we are proposing to test double that number (16) to account for additional variance that may be present in our test data.

A maximum of 20 subjects will be recruited for this study. This is increased from the target 16 subjects to account for any drop-outs, etc.

6. Participant Eligibility

Lower limb amputees will be identified who meet the following inclusion criteria: must be 18 -89 years old, be willing and able to complete the tasks outlined, have no symptoms consistent with peripheral neuropathy or other sensory diagnosis that could prevent them from feeling the temperature of their limb as determined by self-disclosure and/or the Semmes-Weinstein monofilament test and confirmed by clinical judgement, are at least 6 months on a definitive prosthesis, and can understand English in order to be properly consented and provide their feedback to the study personnel. Subjects can be excluded at the discretion of the investigator for other unforeseen disqualifying criteria (such as specific cognitive issues, etc.).

Subjects in this study will not be discriminated by sex or race.

The risks to pregnant women and fetuses are unknown and therefore pregnant women should not participate in the study and will be screened by self-disclosure.

7. Study Methodology

Visit 1: During the first visit, the subject will be consented and enrolled in the study. Measurements and molds will be taken of the residual limb so an experimental socket can be fabricated. For the purposes of this study, the prosthetic liner is being standardized and all subjects will be provided with a prosthetic liner of the proper size, such as an Iceross Comfort Liner by Ossur or the Superior Performance Liner by ALPS, that has been deemed appropriate by a certified prosthetist. Similarly, if a subject typically uses prosthetic socks, they will be provided with a standardized gel sock instead, such as the Silosheath gel sock by Silipose, of the proper size that has been deemed appropriate by a certified prosthetist. The experimental socket would be created to fit the subject while wearing the gel sock (if applicable) and standardized liner using standard clinical socket fabrication techniques. While the ICE units will be fabricated at LTI and Vivonics, each test site will fabricate their own prosthetic sockets and install the ICE units in them.

At this time, the subject's usual socket would be fit with an activity monitor (such as the StepWatch™) to measure the use of the prosthesis and temperature sensors (such as the iButton) on the exterior of the socket to monitor the ambient temperature and on the interior of the socket/liner to monitor the intrasocket temperature. The Thermochron family of iButtons are tiny, durable data loggers that monitor time and temperature that have been used clinically and in take-home research studies in the O&P field. The StepWatch is an activity monitor/step counter that has been shown to have excellent accuracy at slower gait speeds typical of lower limb amputees. These measures would be used as reference measures to confirm the activity of the user in the OFF condition (i.e., with the placebo ICE unit installed later in the study) is similar to the subject's activity when wearing his/her usual, everyday socket.

The subject would wear their newly instrumented usual socket at home for 1 month while the experimental socket is being fabricated. During this time, the subject will be asked to give feedback on the thermal comfort and perspiration in the socket. The feedback will be obtained via a paper log on which the subject enters daily feedback on thermal comfort and perspiration over the course of the month. A research coordinator will be calling subjects periodically to remind them to fill out the log and answer any questions that they may have.

This visit will take up to 2 hours.

Prosthetist Visit: As part of the standard of care when fabricating a new prosthetic socket, the prosthetist first creates a check socket with which to test the fit on the subject before fabricating the definitive socket. Therefore, the subject will be asked to meet with the prosthetist to try on the check socket for fit and alignment.

At the same time the prosthetist fabricates the socket, he may also create a clear, limb "template" similar to the check socket that matches the limb without accommodating any liner or socks (skin fit). This template allows the location of the sensors on the limb to be marked on the template so that the sensors can be placed in the same location on the limb for each lab test visit. The subject may also try on the template for fit during this visit.

This visit will take up to 2 hours.

Visit 2: At the end of one month, when the experimental socket has been fabricated and instrumented, the subject will return to the lab for a second visit. Initially, the subject will be asked to complete a quality of life (QoL) assessment with respect to their current socket, again as a basis for comparison with the experimental socket. The assessment includes the following validated and verified measures: five subscales of the Prosthesis Evaluation Questionnaire (PEQ): Appearance, Frustration, Residual Limb Health, Sounds, and Utility, and two subscales of the Patient Reported Outcomes Measurement Information System (PROMIS): Ability to Participate in Social Roles and Activities Short Form 8a and Satisfaction with Social Roles and Activities Short Form 4a. In addition, a custom survey developed specifically to assess the ICE system will also be given.

In-Laboratory Evaluation: The subject will then perform in-laboratory testing to determine the effectiveness of the ICE system at cooling the residual limb in a controlled environment. The order of conditions (ICE system ON versus OFF) will be randomized.

Similar to what was done in a prior protocol under the previous effort (NEIRB # 120160413/ HRPO Log A-17885.2), an array of temperature sensors will be attached to the subject's residual limb before donning the socket and/or liner to give a more complete picture of the overall temperature distribution across the residual limb. Baseline readings will be taken of the residual limb temperature, the body's core temperature via an oral thermometer and the ambient temperature.

In addition, we will measure the amount of sweat produced during each condition. The limb will be dried with a towel, so pre- and post-activity weight of the liner and towel will be measured and the difference in weight is attributed to the sweat produced during that condition as described by Wernke, et al., (2015). Testing may also be performed in a thermal chamber that regulates the temperature of the testing area, such as that used by Klute et al. (2017), to ensure that the subject will perspire.

The subject will be asked to do the following tasks, similar to Klute et al (2014): (1) an initial seated rest for up to 60 minutes to obtain baseline in-socket temperature data; (2) an activity to increase their body temperature, such as walking on a treadmill [Huff 2008; Klute 2014] or riding a stationary bicycle [Wernke 2015] depending on what the subject is capable of doing, for up to 30 minutes; and (3) a final seated rest for up to 60 minutes. The ICE unit (or placebo unit if it is an OFF condition) will be turned on during thecourse of the testing. Once the final task is complete, the socket and liner will be removed to make the sweat measurement. If the limb and core temperature have not returned to baseline values, then the liner will remain off to facilitate the cooling. The second condition will begin once baseline temperatures have been reached and the test procedure repeated. We expect to demonstrate that even if the socket doesn't reduce the temperature during walking, it can cool the socket immediately upon cessation of walking, unlike the standard socket that produces the sustained high temperatures observed by Klute, et al. (2014) and Huff, et al. (2008).

Throughout the in-lab test sessions, photos and/or videos may be taken to document such things as the location of the sensors on the limb, the temperature gradients across the limb (with a thermal camera), etc. At the end of each condition,

subjective feedback on the comfort and cooling of each condition will be obtained via a questionnaire developed during this effort. The participants would fill out the survey rating parameters such as perceived comfort, intrasocket temperature, noise of the socket systems, etc.

Take-Home Testing Setup: After the laboratory testing is complete, the subject will be sent home with the experimental socket that has the ICE system installed. The order of test conditions ('ON' or 'OFF') will again be randomized, with the subject wearing the socket in the first condition for 1 month then wearing it in the second condition for 1 month, for a total of two months of experimental socket wear time. Subjects will be given instructions regarding how to use and charge the ICE system, along with a phone number of an investigator to call if they have any questions. In addition, in case at any point the subject has an issue with the experimental socket, they will be sent home with a back-up device (typically their usual socket set up with a prosthetic foot which will be provided for them if they don't have one), which would give them the ability to come into the test site for the necessary repairs or changes if the experimental system could no longer be worn.

The experimental socket will be fit with a variety of sensors, such as: the same activity monitor / pedometer worn with their usual/everyday socket, temperature sensors on the exterior of the socket to monitor the ambient temperature and on the interior of the socket/liner to monitor the intrasocket temperature, a humidity sensor, and an accelerometer (ACC) to monitor activity in the community. Ideally the temperature sensors in the ICE controller and/or the intra-socket temperature sensors and StepWatch will enable us to easily determine prosthesis wear time. Once again, throughout the take-home test, the subject will be asked to provide feedback on their temperature comfort and any sweat or temperature related issues with their current socket via the paper logs, similar to what was done with the usual socket.

This visit will take up to 5 hours.

Visit 3: At the end of one month, the subject will return to the laboratory for a third visit to repeat the testing performed in the second visit to provide a second measure that will help to reduce the variance of the analyzed data. First s/he will be asked to complete the same QoL assessment given previously, but this time with respect to the experimental socket and ICE system for the condition just tested. Then they will be asked to repeat the activity testing performed in the prior visit. At the end of the in-lab test, the subject will once again be sent home with the experimental socket with the ICE system to test the second condition ("ON" vs. "OFF"). The instructions for the use of the ICE system will be repeated at this time.

This visit will take up to 5 hours.

Visit 4: At the end of the second crossover month, the subject will return to the lab for a 4th visit. First s/he will be asked to complete the same QoL assessment given previously, but this time with respect to the experimental socket and ICE system for the condition just tested. Then they may be asked to repeat the testing performed in the second and/or third visits (for example if getting set up on the experimental socket and training on the ICE system takes too long in Visit 2 that there wasn't enough time to do the lab testing, or we need a third data point to help reduce variance, etc.). The subject will then see the prosthetist to transition back to their usual socket and the experimental socket/ICE system will be returned to LTI.

This visit will take up to 5 hours.

8. Study Conduct

Subjects will be consented and screened for eligibility criteria. If they decide to participate, their usual socket will be duplicated to create the experimental socket and then it will be instrumented with an activity monitor and temperature

sensors. The subject will wear the instrumented usual socket home for the baseline period, then return to the lab to get their experimental socket. The study will consist of two four-week periods of participants using the ICE system at home and logging their use, activity levels, temperatures, and feedback on the system.

Subjects may withdraw at any time by simply telling the investigators they wish to stop their participation.

If a subject withdraws from the study, the data that were collected from them can still be used, and the withdrawn subjects may be replaced with a new subject. Deviations from the protocol that increase risks for subjects will be reported to New England IRB and HRPO for approval prior to being implemented.

Subjects will be compensated $40 per hour for the 5 visits for the in-lab testing and prosthetist visits for a total of $640 per subject. For the take-home testing, each subject will receive $100 for the first month while wearing their usual socket, and then $200 for each month of wearing the experimental socket (1 month for each condition: ON vs. OFF) for a total of $500 per subject. The anticipated total to complete the study would be $1,140.

9. Study Treatment

This is not a treatment study. The purpose of the study is to evaluate the effectiveness of the ICE system.

10. Evaluation of Adverse Events

Based on past testing and data collection, no adverse events are expected. Adverse events could include: discomfort or dermatological reaction to sensors in the socket, tripping while walking on the treadmill, overheating or overcooling due to controller, sensor, or battery malfunction of the ICE unit. These risks have been mitigated by using biocompatible materials and/or hypoallergenic tape with the sensors, using a spotter during walking tasks for in-lab testing, and standard thermal and electrical management techniques including thermal battery management, voltage/current limiting, and monitoring temperature during testing.

All unanticipated problems involving risk to subjects or others, serious adverse events related to participation in the study and subject deaths related to participation in the study will be promptly reported to the New England IRB (NEIRB), MVAHCS IRB, and HRPO. A written description of the adverse event will be stored in the study file maintained by the Principal Investigators. Also, the protocol will be reviewed in light of the adverse event to determine if modifications need to be made to prevent the event from occurring again. Major modifications to the research protocol and any modifications that could potentially increase risk to human subjects must be submitted to the NEIRB, MVAHCS IRB, and HRPO for approval prior to implementation.

11. Ethical Considerations

There is no direct benefit to the user. Participating in this study may potentially advance the scientific community's understanding of the effect of cooling intra-socket temperatures on the activity, comfort and quality of life of lower limb amputees.

The protocol, consent form, and recruitment flyer will require IRB review and approval. The principal investigator will be in continuous communication with the IRBs and HRPO and will forward information to the co-investigators. Subjects' participation is voluntary and they may withdraw from participation in the study at any time by simply telling any one of the investigators that they wish to stop. The investigators may choose to terminate a subject's participation if he or she experiences discomfort or injury. In addition, participants will be given any new information which is discovered during the course of the study which may influence participants' willingness to continue the study. If they desire to do so, subjects' will also have the option to discuss any concerns regarding the study activities or the investigators with an impartial staff member of the site IRB, whose duty it is to hear and review such concerns and provide advice or take any other appropriate actions.

The investigators will ensure the anonymity of all participants in this study. After completing the consenting process, subjects will be assigned a random identification number. The number will be used on all test data associated with the subject. No personal identifiers will be associated with the data collected from the subjects during the various tests. The PI will have a master document linking the subject name with ID number, and it will be stored on a password protected computer, with only the PI and approved study staff having access to the master list. Test data will be kept at Liberating Technologies, Inc., MVAHCS, and Vivonics and stored in a secure manner depending on the media: either a password protected computer with access limited to the co-investigator, or in a locked filing cabinet in the investigator's office. A copy of the test data will also be retained by the PI in the program folder, also stored in a secured manner.

12. Study Monitoring and Oversight

The oversight of the study falls on the co-investigators. They will be responsible for ensuring the study follows the approved protocol and for reporting any deviations or adverse events that occur during the study to New England IRB and HRPO. De-identified data, photos, and videos will be kept indefinitely to show in scientific presentations and publications. Photos will not contain any identifying information about the subject. The photographs will not include the subject's face or any identifying marks such as tattoos. If identifying photographs happen to be received from a subject, they will be de-identified by either cropping or blurring using photo-editing software.

Additionally, representatives of the United States Army Medical Research Acquisition Activity (USAMRAA) are eligible to review research records as a function of their responsibility to protect subjects in research.

13. Investigational Product Management

The ICE technology tested in this study is cooling device for the residual limb that is an add-on system to a standard prosthetic socket. Additionally, commercially-available activity monitors and temperature sensors may also be used in the instrumented sockets.

INTRASOCKET COOLING ELEMENT

The ICE active cooling module is comprised of a combination of: 1) an inner Heat Spreader (isothermal) layer designed to maintain approximately constant temperature along a section of the inner wall of the socket and 2) a Heat Extractor providing a heat channeling pathway utilizing: a) a Thermo-Electric Cooling (TEC) module, b) a heat radiator (heat sink) structure and c) an air circulating system (fan) to discharge the heat to the surrounding air.

The heat spreader functions to collect heat from around the circumference of the limb and then route it to a much smaller and more focal point where it is expelled from the socket by the heat extractor. Additionally, the system has been developed to work in conjunction with commercially-available prosthetic liners where the heat spreader is in contact with the liner, not the skin, and pulls the excess heat through the liner to extract it.

The active heat pumping mechanism that is used in these devices is a thermoelectric cooler (TEC). TECs are semiconductor devices that use electrical current to pump heat (Q) from one side of the device to the other based on the Peltier effect. As an active system, a TEC can chill the heat source (residual limb) to a temperature lower than its surroundings. In the ICE system, the TEC is used to pump heat from the heat spreader to a heat sink acting as a radiator. The TEC raises the heat sink to a temperature above ambient. A fan then facilitates removal of heat from the heat sink. The TEC heat pumping action is particularly useful in high ambient temperature situations where the heat sink and fan alone would not be able to sufficiently cool the cold side of the heat spreader.

The ICE unit is powered by a standard, commercially-available 2 cell Li-ion rechargeable battery pack, such as the Tenergy 18650 7.2V 3500mAh battery, and is housed in a case to protect against damage. This battery has protection circuitry, including over-charge, over-discharge and short-circuit protection, and is being charged with the recommended charger externally, off the subjects. Control of the device is based on push buttons where the user engages the button when he/she feels that cooling in necessary and turns off the system when he/she no longer needs cooling. When the device is on, the system will to regulate cooling to the limb based on feedback from multiple sensors in the device, including the hot and cold side temperatures of the TEC. As long as the cold side of the TEC is above the minimum threshold, the TEC will be powered to reduce the limb temperature while taking into account battery life. As the cold side temperature approaches the threshold temperature, the voltage to the TEC will be reduced to maintain a TEC cold side temperature above the threshold. Prior studies have shown that applying cooling at a temperature of 22°C (72°F) is the lowest temperature that is uniformly well-tolerated [Aishwarya 2016]. Because we will have a prosthetic liner between the ICE cooling element and the skin, we will use a cold side threshold temperature that takes into account the thermal properties of the standardized liner to ensure a residual limb temperature of no less than 22°C. Our testing has shown that the cold side threshold can be as low as 13°C (55°F) and still maintain a skin temperature of greater than 22°C. Therefore, based on this data we will use 13°C as our minimum cold side temperature threshold; however, we may iterate the control algorithm and adjust the threshold as needed as more data is collected that can inform the algorithm.

SOCKETS

The prosthetic interface used in this study will be fabricated by a Board Certified Prosthetist, following conventional standardized methods. The “ICE System” is to be incorporated into the socket design with manufacturing techniques similar to those used to integrate commercially-available prosthetic components and add-ons, such as suction valves, shuttle locks, elevated vacuum systems (e.g. Ohio Willow Wood ONE system), etc. The inclusion of the “ICE System” will be such that the structural integrity and functionality of the socket will not be compromised. The socket characteristics will be similar to the subject’s usual socket, monitoring and maintaining acceptable mobility and comfort throughout the testing procedure.

LINERS

The liners tested in this study will be commercial-off-the-shelf (COTS) products that are approved for the general population. While the ultimate ICE system could work with a variety of prosthetic liners, we have standardized the liner used for this study in order to eliminate confounding factors of liner material and thickness.

PROSTHETIC SOCKS

The prosthetic socks in this study will be commercial-off-the-shelf (COTS) products that have been identified to work well with the ICE system.

ACTIVITY MONITORS

Commercial activity monitoring devices such as the StepWatch will be used to record how many steps the subject has taken and may also be used to help determine when the subject is wearing his/her prosthesis.

TEMPERATURE SENSORS

Commercially available temperature sensors, such as thermistors, thermocouples and iButtons, may be used to monitor the temperature of the ICE device as well as the temperature of the residual limb inside the prosthetic socket. The thermistors and thermocouples have been used in the approved protocols for the previous and current studies (NEIRB # 120160413/ HRPO Log A-17885.2). The iButton has been used in O&P clinical practice and research studies to monitor temperatures within O&P devices (Felton 2015].

SILICONE

Ibutton (or similar) temperature sensors may be embedded into the standard liner in order to monitor limb temperature in the socket while at home. LTI has developed a process to do this and will be embedding all sensors for this test protocol. The process starts with casting a square of biocompatible silicone, such as Smooth-on's certified skin safe Ecoflex 00-30 series, over an iButton. A square of the same size is then cut out of the silicone surrounding the inner liner. Once the Ecoflex (or similar material) cures, the iButton is placed into the cut-out in the liner and bonded to the walls using a medical grade adhesive, such as Elkem's Silbione RTV silicone adhesive.

14. Data Analysis

The data collected in the laboratory and in the take-home portions of this study will include limb temperature, ambient temperature, activity (steps), ICE system use time (collected via the written log and the ICE unit), and standard outcomes measures for both the usual socket, and ON and OFF conditions. Standard outcomes measures will include: PEQ (subscales for Appearance, Frustration, Residual Limb Health, Sounds and Utility) and the PROMIS (the Ability to Participate in Social Roles and Activities Short Form 8a, and the Satisfaction with Social Roles and Activities Short Form 4a). A custom survey was developed to assess the ICE system and will also be used.

The primary outcome of this study will assess the effect of the ICE system on the temperature of the residual limb; however secondary measures include activity level and satisfaction with the prosthesis using the above measures. Measures during the cooling condition (ON) will be compared to the control (OFF) condition and the baseline (Usual Socket) condition.