Title: Novel Lower-Limb Prostheses: Comparing Adherence, Perspiration, and Residual Limb Skin Health in a Hot, Humid Environment and During Activities of Daily Living

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Human Subjects Protocol

VA Puget Sound IRB

Novel Lower-Limb Prostheses: Comparing Adherence, Perspiration, and Residual Limb Skin Health in a Hot, Humid Environment and During Activities of Daily Living

MIRB #01695

Funding Agency: Department of Defense and Department of Veteran Affairs

Principal Investigator: Glenn Klute, PhD

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Abstract

Background: Individuals with lower limb amputation often complain about uncomfortable residual limb skin temperatures and the accumulation of sweat inside their prostheses that occurs when they participate in vigorous activities. In many circumstances, inadequate moisture management is more than bothersome, it can significantly limit or inhibit their mobility. It doesn't take long before the presence of sweat on the residual limb causes the prosthesis to feel unstable, like it may slip off. If the situation allows, people often remove their prosthesis before it falls off, wipe it and the residual limb dry, put it on again, then continue their activity. Another option is to reduce the intensity of activities before sweat becomes a problem. Both options are disruptive.

The objective of this study is to compare two different types of lower limb prosthetic systems that remove sweat (one new commercially-available system and one experimental system that uses an experimental liner and suspension with a standard socket and commercially-available foot) with the participant's own "as prescribed" prosthetic system. We aim to determine which one provides people, who are very active or work in demanding environments, with a secure fit despite a significant amount of residual limb sweating and does so without compromising residual limb health and comfort. The two study prosthetic systems that remove sweat are: 1) a new, commercially-available, perforated elastomeric liner intended to transport perspiration away from the skin (Uniprox's SoftSkin Air) and 2) an improved version of the Dynamic Air Exchange (DAE) prosthetic system we developed, the Dynamic Air Exchange - Rising Edge Design (DAE-RED). Anecdotal reports suggest the perforated liner can maintain a secure fit/suspension during periods of significant sweating but may result in excessive skin dryness and discomfort. The DAE-RED expels sweat using a vacuum pump like its predecessor but incorporates a body-weight activated pump to minimize battery consumption and a revised ventilation system that removes the need for undesirable exterior tube connections.

Purpose: The purpose of this study is to compare two different, lower limb prosthetic systems purported to remove sweat and the participant's own "as prescribed" system to identify which is most effective at maintaining limb skin health and a secure fit, when worn in conditions that result in a significant amount sweating. We will also compare how comfortable the three prostheses are when participants do their usual activities while at home, work, and in the community.

We hope this work will result in widespread adoption of the prosthesis that maximizes adherence to the residual limb in demanding environments while maintaining the health and comfort of the limb. Improving prosthetic adherence will expand the conditions under which individuals with lower limb amputation can confidently work despite significant sweating. Improvements in prosthetic limb adherence are especially relevant to younger, more active Veterans and individuals still on active duty, who have an amputation.

Methodology: We will enroll up to 40 individuals with a below-knee amputation on only one side, who use their as-prescribed prosthesis on a regular basis. Three different prosthetic systems will be

compared: (1) their as-prescribed prosthesis, (2) a new-to-market prosthesis with a unique liner with holes in it that allows sweat to flow away from the skin, and (3) a novel prosthesis that has a body-weight activated pump to create air flow between the prosthesis and the skin. After baseline and prosthetic fitting visits, participants will be randomized to use one of the two study prostheses during their normal daily activities for 2-weeks and then return to the VA for a data collection visit. This process will be repeated with their as-prescribed prosthesis, and then with the other study prosthesis.

List of Abbreviations

AE – adverse event

CDMRP – Congressionally Directed Medical Research Programs

CPRS - Computerized Patient Record System

CRQ – Continuing Review Questionnaire

DAE – Dynamic Air Exchange

DAE-RED – Dynamic Air Exchange–Rising Air Design

DOD – Department of Defense

HIPAA – Health Insurance Portability and Accountability Act

ISO - Information Security Officer

IRB – Institutional Review Board

ORP HRPO – Office Research Protection Human Research Protection Office

PHI – Protected Health Information

PI – Principal Investigator

PIN – Distal Locking Pin Suspension

PTB – Patellar Tendon Bearing

PO – Privacy Officer

RAC – Regional Amputee Center

ROP – Report of Other Problem

SAE – Serious Adverse Event

UW – University of Washington

VA – Veterans Affairs

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1. Key Study Personnel

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2. Introduction

Individuals with lower limb amputation often complain about uncomfortable skin temperatures and the accumulation of perspiration inside their prostheses [1]–[6]. Even relatively light activities like walking, which are far below the vigor of warfighter activities, can cause substantial increases in residual limb skin temperatures [7], [8]. Even when interspersed with periods of rest, the cumulative effect over the course of a typical day is a gradual increase in skin temperature [9]. As skin temperatures increase, the physiological response includes both vasodilation and sympathetic stimulation of the limb's sweat glands [10]. Vasodilation increases blood flow to the skin surface and would allow heat loss to the environment if the thermal properties of prosthesis [11] did not prevent it. Likewise, the onset of perspiration can often provide cooling through evaporation depending on the environment's relative humidity, but is again prevented by the prosthesis [12]. In terms of adherence, a little perspiration can increase the coefficient of friction [13], [14] between the prosthesis and the limb, but if perspiration continues, a threshold is exceeded [15], [16] where the prosthetic suspension is no longer secure. Many amputees can sense the impending loss of adherence during vigorous activities and are able to stop, doff the prosthesis, wipe it and the limb dry, and then don it again. However, not in all situations due to limitations in the environment, activity, or even social stigma.

The occurrence of perspiration can be modulated by several well-known factors. First, the vigor or intensity of activity is directly proportional to the amount of heat generated by the body. Increases in locomotion speed, terrain slope, or amount of load carriage are well-studied methods to increase intensity [17]–[23]. Many circumstances allow the civilian with lower limb amputation to reduce the intensity of their activities and limit perspiration. However, the warfighter with a lower limb amputation may not be presented with such an option.

Second, elevated body temperature and perspiration can be modulated by behavioral choices, such as doffing insulative clothing. Unfortunately, the thermal properties of the prosthetic liner and socket impede direct conduction of heat from the residual limb to the environment. Tests measuring the thermal conductivity of 23 different commercially-available liners and two common socket materials found all were highly insulative [11]. Evaporation of perspiration typically cools excessively warm skin temperatures; however, lower limb amputees are deprived of this cooling mechanism as well. A study measuring the amount of moisture that could be evaporated through the prosthetic liner found little to no moisture could permeate the elastomers [12]. Lower limb amputees have limited behavioral options to reduce or stop perspiration as they simply cannot remove their prosthesis and remain ambulatory.

Third, the local environment temperature and humidity are important as the body must dissipate activity-generated heat to the surroundings. Environment conditions vary significantly around the world, but locations of potential military and political significance can be quite warm and humid (see Table 1). Summertime conditions can often reach 35 °C (95 °F) and 50% relative humidity. These hot and humid conditions can make it difficult to dissipate activity-generated heat.

One approach to maintaining a secure adherence under perspiration-inducing conditions is to keep skin temperatures below that where perspiration begins. Webber and Davis [24] presented a half-size 3D printed model with a helical channel in the socket wall to cool the residual limb. Ghoseiri et al. [25] constructed a socket with a thermoelectric heat pump coupled to an aluminum heat transfer structure integral with the socket wall. Han et al. [26] used heat pipes to conduct heat to a compact heat sink where a fan could convect heat from the prosthesis to the surroundings. Wernke [27] tested a liner with phase change material and found residual limb skin temperatures to be lower at the end of an exercise bout, and for patients that perspired, less accumulation compared to a liner without phase change materials. Unfortunately, these designs all rely on cool or dry environments which may not be the surroundings of the warfighter amputee.

An alternative approach to maintaining a secure adherence is to remove perspiration from the residual limb skin as it accumulates. One method, using a perforated elastomeric liner, allows perspiration to be exuded into the liner-prosthetic socket interstitial space. Two suspension systems using this method have recently come to market (Uniprox Softskin Air, Uniprox GmbH, Zeulenroda-Triebes, GER; Endolite Silcare Breathe; Endolite US, Miamisburg, OH).

The *target population* of the proposed research is the veteran lower limb amputee. In 2002, 82,000 Americans had a lower limb amputation arising from complications associated with diabetes [28], the direct U.S. hospital costs related to these procedures could be conservatively estimated to exceed $350M annually [29]. Available data suggests the VA performs between 3000 and 5000 lower limb amputation surgeries on veterans of diabetic and dysvascular etiology each year [30], [31]. These veterans are among the 623,000 Americans who live with a major lower limb amputation [32], a population whose growth due to diabetes doubled between 1990 and 2008, but has since fortunately

plateaued [33] despite an aging and overweight population. An additional cohort of Veterans stems from the U.S. involvement in the enduring military conflicts overseas (e.g., n=1795 major limb amputation (all causes) from 2000 to 2011[34]; n=1645 major limb amputation (battle injuries) from 7Oct2001 to 1Jun2015 [35]). These individuals tend to have few comorbidities and may be expected to rely on the VA for the rehabilitative care for many years to come.

The results from this study will reveal the readiness and capacity of individuals with lower limb amputation who work, or want to work, in demanding environments. It will set a benchmark for the current standard-of-care and may show the benefit of new devices. We anticipate the results will benefit all individuals with lower limb amputation independent of amputation level (below-, thru-, or above-knee) or the cause of amputation (trauma, diabetes, tumor, congenital).

The *clinical significance* of project will be achieved in widespread adoption of the prosthesis that maximizes adherence to the residual limb in demanding environments while maintaining a healthy and comfortable residual limb. Further, by also expanding the conditions under which individuals with lower limb amputation can confidently work despite profuse sweating.

3. Specific Aims and Hypotheses

Specific Aim 1

Compare three different, lower limb prosthetic systems and identify which is most effective at maintaining a secure adherence when worn in conditions that result in profuse perspiration.

Our hypotheses related to the first specific aim include:

$H_{1.1}$ The amount of slippage (loss of adherence) will be different between the three prosthetic systems. Measurements of the prosthetic liner position relative to the residual limb will be recorded (before and after) and the differences will be compared.

$H_{1.2}$ The amount of perspiration expelled will be different between the Uniprox and DAE-RED. Tare weighing (before and after) of all prosthesis components will be performed and the remainder, after subtracting the amount accumulated inside, will be compared.

Specific Aim 2:

Compare how three prosthetic systems effect residual limb skin health and comfort when participants pursue their usual activities in the home, work, and community environments.

Our hypotheses related to the second specific aim include:

$H_{2.1}$ Residual limb skin hydration will be different between the three prosthetic systems. After doffing the prosthesis, we will use a specialized instrument (Corneometer) to measure skin hydration, a measure of skin dryness. The results between prostheses will be compared.

$H_{2.2}$ Residual limb transepidermal water loss will be different between the three prosthetic systems. After doffing the prosthesis, we will use a specialized instrument (Tewameter) to measure transepidermal water loss, a measure of skin barrier disruption. The results between prostheses will be compared.

$H_{2.3}$ The Socket Comfort Score will be different between the three prosthetic systems. Individuals can have strong opinions about their prosthesis. To assess comfort, we will ask subjects to rate their socket comfort on a 11-point scale, and the results between prostheses will be compared**.**

4. Resources and Personnel

Data collection procedures for this study will be conducted at the VA Puget Sound in Seattle, WA. See Study Staff Sheet attachment for listing of personnel, ability to obtain consent, and access to PHI.

Under the supervision of the PI, the Research Coordinator and/or other designated study staff will be responsible for conducting recruitment, consent and scheduling study procedures. The PI, Investigators, and/or Research Engineers and assistants will conduct procedures with participants. The PI, Investigators, and the Biostatistician will be primarily responsible for data analysis and interpretation; Research Engineers and assistants may also assist with this. Under the supervision of the PI, the Program Coordinator and/or other designated study staff will be responsible for IRB related matters.

5. Study Procedures

5.1 Study Design

We will enroll up to 40 individuals with a below-knee amputation on only one side, who use their as-prescribed prosthesis on a regular basis. Three different prosthetic systems will be compared: (1) their as-prescribed prosthesis, (2) a new-to-market prosthesis with a unique liner with holes in it that allows sweat to flow away from the skin, and (3) a novel prosthesis that has a body-weight activated pump to create air flow between the prosthesis and the skin. After baseline and prosthetic fitting visits, participants will be randomized to use one of the two study prostheses during their normal daily activities for 2-weeks and then return to the VA for a data collection visit. This process will be repeated with their as-prescribed prosthesis, and then with the other study prosthesis.

See section 5.5 below for data collection procedures.

5.2 Recruitment Methods and Initial Screening

Up to 200 individuals may be approached during recruitment and enrollment procedures. Please note that all references in this section to in-person contact/initial-screening will follow the *Screening Script* attachment, all references to approach letters and postcards refer to the *Recruitment Letter* attachment.

Medical Record/Database: Letter/Phone/In-person

Designated research staff will screen relevant clinic lists in CPRS (amputee rehabilitation, prosthetics, amputee support groups), and the Regional Amputation Center (RAC) database file (this is a clinical database that includes a list of patients with an amputation who receive care the VA Puget Sound) to identify potential participants.

After review of relevant clinic lists in CPRS and the RAC file, designated staff will go to the clinic or contact providers on the phone or via encrypted VA email to ask if a patient might be a good fit for the study. If the clinician agrees that a patient may be an appropriate study participant, during an appointment the clinician will ask the patient if she/he is interested in speaking with designated study staff; patients will be given a chance to opt out. For patients who are interested, designated study staff will speak to potential participants directly after a clinic visit and/or use CPRS or the RAC file to obtain potential participants' contact information (i.e., name, address, telephone number). For potential participants who learned about the study in person but may not have time to complete the eligibility screening with us, designated study staff may give them a flyer and/or business card and make a follow-up approach phone call and/or send an approach letter. If potential participants are unable to meet with designated study staff in-person then we will send an approach letter.

We may also search CPRS ,the RAC database file, and the Corporate Data Warehouse (CDW) to identify individuals with a qualifying lower limb amputation and mail them the approach letter.

If potential participants have not spoken with us within 14 days of the first call and/or mailing the approach letter, designated study staff will contact them by phone up to two more times (three times total) about this study. The approach letter will also in

clude an “opt out” postcard. The opt-out postcard will have a unique study recruitment identification code. If an individual returns the postcard to opt out they will not be approached about this study again.

Clinician Referral

Designated staff will inform providers working in relevant clinics about the study and inclusion/exclusion criteria so they can refer potential participants to contact the study team. Flyers and business cards may be provided to clinicians to give to patients that are interested in the study. If a clinician informs patients about the study and the patient agrees to be contacted about it, the clinician may provide us with the patient’s name (via encrypted email/in-person/on the phone). We will look up the patient’s contact information in CPRS and make an approach call (in this instance – we will obtain printable documentation from the clinician, via encrypted email or a note in the medical record, that the patient agreed to be contacted on the phone).

Flyers/Text

Flyers may be posted in designated areas at the VA Puget Sound (Seattle and American Lake) on the CCTV system and in publicly accessible locations in the community (e.g., public libraries, community centers, coffee shops). Flyers and study staff business cards will also be posted and distributed to potential subjects at clinics in the community *(copies of the letters of support will be submitted to the IRB as miscellaneous submissions, as they are obtained);* clinicians and support staff will direct interested individuals to contact us to learn more about the study. The flyers may also be re-sized to be used in print publications or as a complete image in online ads. We may post classified ads in print and online publications. We may also post the classified ad text to our Center’s webpage.

VA Puget Sound Center Registry: Letter/Phone

At the VA Puget Sound, designated study staff may also identify potential participants using the VA Center for Limb and Mobility Subject Registry (PI: Klute, #00433). The Registry contains contact information for participants who were screened for and/or participated in previous studies with our

research group and agreed to be contacted (via phone call and/or letter) for future studies. Designated study staff may make an approach phone call and/or send an approach letter to potential participants asking whether they are interested in the study. If potential participants have not spoken with us within 14 days of the first call and/or of the mailing the approach letter, designated study staff will contact them by phone up to two more times. The approach letter will also include an "opt out" postcard. The opt-out postcard will have a unique study recruitment identification code. If an individual returns the postcard to opt out they will not be approached about this study again. Interested individuals will be screened for eligibility. Designated study staff may also speak with these potential participants in-person if they have an upcoming clinic visit.

Eligibility Screening

Interested individuals will be screened for eligibility in-person or over the phone; see attached screening script.

Recruitment Activities at UW/Harborview

A confidentiality agreement will be obtained for this activity; the UW does not consider itself "engaged" for the recruitment activity described below, please see attached engagement worksheet.

Designated VA study staff may screen relevant UW/Harborview clinic lists, appointment calendars and patient medical records to identify potential participants with a qualifying amputation. Study staff may also attend clinic at these facilities to identify and/or contact potential participants. Before or after clinic, study staff will discuss with the clinician any patients that might be appropriate candidates. If the clinician agrees that the study may be a good fit for a patient, the clinician will ask the patient if she/he is interested in speaking with study staff. For patients who are interested, study staff will speak to potential participants directly during/after a clinic visit to tell them about the study, give them a study flyer, and/or request their permission to screen them for initial eligibility (via the VA IRB approved Screening Script) and provide this information to the VA. If potential participants are screened for initial eligibility in person, study staff will label the noted responses with a recruitment id code and no HIPAA identifiers or sensitive health information will be noted on the form. Study staff will transport the forms to the VA for storage. If patients are interested in learning about the study and/or in doing the initial screening but are unable to meet in person with study staff, we will look up the patients' contact information in their medical record and contact them on the phone and/or send them the VA recruitment letter (the VA IRB approved letter with VA contact information would be sent per the process described above).

Staff may also search/access UW/Harborview medical records to identify individuals with a qualifying amputation, obtain their contact information (i.e., name, address, telephone number) and mail them the approach letter.

Clinician Referral

Designated VA staff will inform providers working in relevant clinics about the study and inclusion/exclusion criteria so they can refer potential participants to contact the study team. Flyers and business cards may be provided to clinicians to give to patients that are interested in the study. Clinicians may also provide us (via in-person/on the phone) with the names of patients that they are aware of who may be a good fit for the study and we will look up their contact information to send an approach letter.

Also, for potential participants who were initially contacted via letter and/or in-person but have not yet completed the initial screening, study staff may provide the potential participants' contact information and limited pre-screening criteria over the phone to other study staff at the VA who will enter it into the screening log for tracking and follow up. This information may also be added (via VA remote access) to the screening log maintained on the VA server. Study staff will follow up with potential participants based on the VA approved protocol.

5.3 Informed Consent Procedures

A waiver of informed consent and HIPAA authorization will be used for recruitment and screening purposes. A waiver of documentation of consent and HIPAA authorization will be used to retain the preliminary eligibility screening responses *(see Screening Script)*. Informed consent will be obtained prior to enrollment in the study.

The Research Coordinator, the PI, and/or other designated staff, as indicated on the study staff form, will conduct the informed consent process. All study personnel will complete the necessary human subjects protections training per VA policy.

5.4 Inclusion/Exclusion Criteria

Inclusion Criteria:

1) Age 18-79 years
2) Unilateral transtibial amputation
3) Been fit with a prosthesis and used it for at least 6 months
4) Wear the prosthesis for 4 or more hours on average per day
5) Ambulate without upper extremity aids
6) Able to walk for 30 minutes on a treadmill

Exclusion criteria:

1) Improper fit and suspension with current prosthesis and one cannot be achieved with clinical resources (determined at initial visit)
2) Current skin irritation or injury on residual limb
3) Osteoarthritis, injury, or pain that interferes with walking ability
4) Currently incarcerated
5) Pregnant (determined via self-report)

6) Inadequate cognitive function or language proficiency to consent to participate
7) High (>20%) coronary heart disease risk at 10 years as determined by their Framingham Risk Score

5.5 Study Visits, Data Collection

Visits and length of participation

Consent and data collection procedures will be done at the VA Puget Sound in Seattle. Participants will be asked to do 4-7 visits that may span up to 2 months. If we find that data are missing or corrupt participants may be asked to do another study visit. All procedures are for research purposes and provide no clinical treatment. Participants will be provided rest breaks throughout the procedures and may request one at any time. We may call and/or email participants to remind them about upcoming study visits. Participants will be asked to not consume caffeine, tobacco, and alcohol for two hours prior to each visit and not apply anything to their skin for 12 hours before the visit.

Data Collection Protocol

Baseline Visit

Demographics
We will ask participants to provide us with the following demographic information:

- age
- years since amputation
- side of amputation
- cause of amputation
- body weight
- height
- as prescribed prosthesis (socket type, liner, suspension system, foot type, category and size)

Skin Health and Socket Comfort

To collect baseline data, participants will be asked to take off their prosthesis while seated in a climate-controlled room set to 68 °F/20 °C, 50% relative humidity. Their residual limb will be dried with a towel (if needed). After sitting for 15 minutes, we will use specialized equipment to measure participants' skin health (skin hydration level and transepidermal water loss) by touching a few places on their legs with the instrument's hand-held measurement tools/probes. The average results from these measurements will be the participants' baseline skin health for their as-prescribed prosthesis. If subjects have thick leg hair, we may need to shave a small patch to allow the instrument to get a good reading. Participants will also be asked rate their how comfortable their socket is on a 0-10 scale.

Self-Selected Walking Speed

While using their own prosthesis, participants will be asked to walk back and forth down an unobstructed 65ft/20-m hallway several times. These trials will allow us to determine participants' self-selected walking speed.

Prosthetic Fitting

Our research prosthetist may begin the fitting process for the two study prostheses during the baseline visit, but this process may take place over 2-3 visits. Once both study prostheses fit well, participants will be randomly assigned to wear either the perforated prosthetic liner system or the novel prosthesis during their usual daily activities for two weeks. During the daily use periods, participants will be instructed to check their limb for redness and/or irritation twice a day and if they notice any issues they should contact us immediately for instructions. We will assist with arranging any necessary follow-up care as needed.

Step Count

During the daily use periods, an electronic step counter, taped to the prosthetic pylon/ankle, will collect step-count data. The step data will be collected from the counter when participants return for the next study visit.

Heart Disease Risk Screening Test

During the baseline or prosthetic fitting study visits, prior to the treadmill walk in the 95°F temperature condition, we will screen participants for cardiac problems. We will use the Framingham Risk Score calculator (https://www.mdcalc.com/framingham-coronary-heart-disease-risk-score), an age and sex-specific algorithm that calculates the risk for developing cardiovascular disease at 10 years. Participants who have a high (>20%) coronary heart disease risk at 10 years will be withdrawn from the study. The screening test requires the following information: age, sex, smoker, currently on any medication to treat high blood pressure, systolic blood pressure, total cholesterol, and high-density lipoproteins (HDL) cholesterol. The first four items will be obtained by self-report. Systolic blood pressure will be measured with an existing portable digital blood pressure monitor. Total cholesterol and HDL cholesterol results, from within the last 2 years, may be obtained from VA or UW medical records, another medical facility via a release of records request, participant self-report, or by blood draw at the VAPSHCS clinic. If we determine that a participant's risk of heart problems is too high for this study we will advise them to follow-up with their regular medical care provider, and they will not be able to participate further in the study. If a participant is unable to continue in the study, they will be compensated for their effort.

Visit: Study Prosthesis 1

After two weeks of using the first study prosthesis, participants will return to the VA for a data collection visit. Participants will be instructed to drink approximately 8 to 15 ounces of water two

hours before their study visit and to bring a pair of shorts and a t-shirt to wear, but we will provide this clothing if they prefer. We will repeat the procedures described above in the Baseline Visit to measure skin health and Socket Comfort Score.

While the prosthesis is off, we will make sure the socket and other key components are dry and we will weigh them. Participants will be provided with fresh/dry socks to wear during the procedures. Participants will be asked to change into the shirt and shorts and put the prosthesis back on. A private area to change will be provided. Participants will be asked to wear a wristwatch-style heart rate monitor during the study visit. We will also place a small absorbent pad on the calf of the intact leg to collect sweat. The pad will be attached to the skin using a sticky waterproof covering to prevent evaporation. We will also draw a mark on the skin of the residual limb at the top edge of the socket liner so we can measure how much the liner slips.

When ready, participants will enter the climate-controlled space set at 35° C (95 °F) and 50% relative humidity. Participants will sit for a 30-minute acclimation period and will then be asked to walk on a treadmill at their pre-determined self-selected walking speed for up to 30 minutes or until they feel like the prosthesis may slip off. The duration of activity will be timed, but we anticipate all participants will be able to walk for 30 minutes. Participants will be allowed to drink water as desired during the trial, and we will record the amount of fluid they drink. Handrails and a chair will be present in case participants feel unsteady or wish to take a break.

For safety purposes, we will track participants' heart rate (via the wristwatch monitor) throughout the test. For participants who do not take a beta-blocker medication (self-report), we will stop the test if their heart rate exceeds 75% of their age-adjusted maximum heart rate (220 minus age in years) for 3 consecutive minutes. For participants who do take a beta-blocker medication, we will stop the test if their heart rate exceeds 110 beats per minute for 3 consecutive minutes.

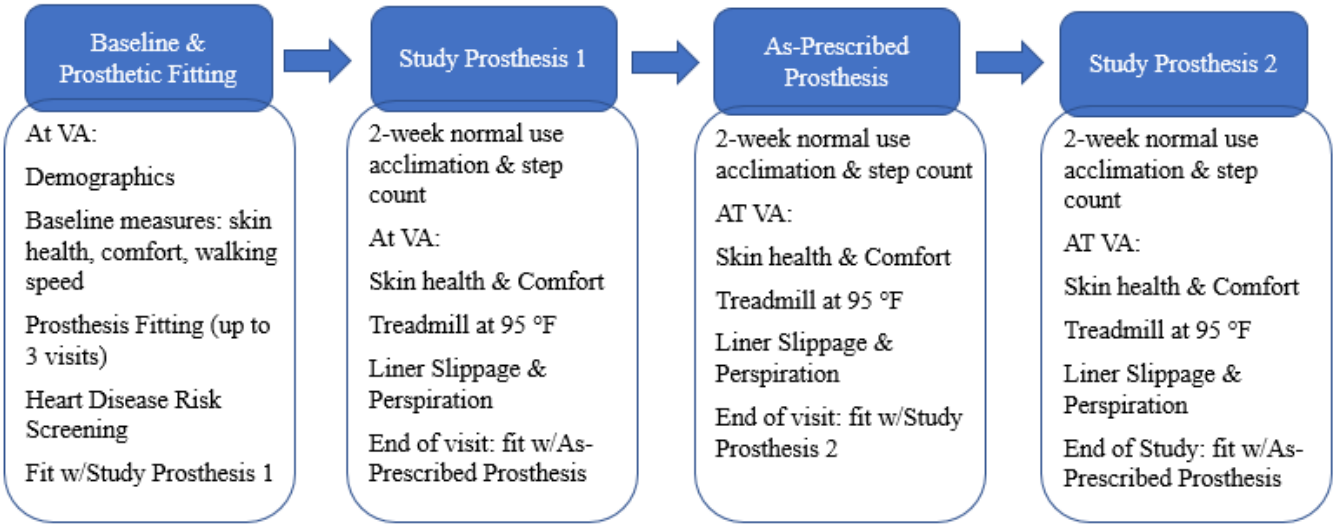
When the treadmill walk is done, we will have participants sit and rest in a space with a comfortable climate (68 °F/20 °C, 50% relative humidity) for up to 30 minutes, and we will measure the prosthetic liner slippage. Participants will be asked to take off the prosthesis and then we will re-weigh the key components. We will also dry off participants' residual limb with an absorbent towel to collect the sweat remaining on the skin and remove the absorbent pad from the other leg. We will weigh the towels, prosthetic components, socks, and absorbent pad to see how much moisture the participants lost on their lower limbs by sweating.

We will put the step counter on participants' as-prescribed prosthesis. Participants will then be fit with their As-Prescribed prosthesis and asked to use it during their usual daily activities for the next two weeks.

Visits: As-Prescribed Prosthesis & Study Prosthesis 2

After the 2-week use period, participants will come back to the VA and, using their As-Prescribed prosthesis, they will do the same procedures they did with Study Prosthesis 1. At the end of the

visit, participants will be fit with the other study prosthesis then repeat the 2-week use period and the data collection visit.



During study sessions, visitors and observers will not be allowed in the lab unless the participant agrees to their presence; the participant can change her/his mind at any time.

Photos and Video

We may take video and photos of participants during portions of this study for documentation and use in research publications. To protect the identity and privacy of our participants, all videos and photos will be edited later to de-identify the images (e.g., blurring of faces, tattoos, and other distinguishing marks). No sound will be recorded to prevent voice identification.

Repository

Participants will be asked if they are interested in allowing their study data to be added to our de-identified data repository so that it may be used for additional research in the future. Participants who are interested will be asked to sign a separate consent form for the repository (MIRB# 00493). Once the consent form is signed, and after a PRAF to MIRB# 00493 to accept the data has been approved, a copy of the data will be added to the repository on an ongoing basis throughout the course of the study.

Payment to Participants

Participants will receive $600 for participating in the study. Participants will be paid after their participation in the study is finished. Payments will be made by check. Checks will be mailed out 2-8 weeks after participants' last visit or they can make arrangements to pick up their payment at the VA Puget Sound within the same timeframe. If participants are screened out or withdraw prior to finishing all study procedures, we will compensate them on a prorated basis based on the number of visits/how many of the study procedures they completed.

5.6 Risks and Risk Management

Please note, the increase in physical risks associated with participation in this study only represent a small increase from those encountered in daily life of the participant population.

It is possible that participants may experience an injury (e.g., arising from a trip or a fall while walking on a treadmill or while wearing a study provided prosthesis during the at-home acclimation periods) and/or discomfort (e.g., mild to moderate muscle soreness, excessive skin dryness, blisters, or other soft tissue irritation while in the lab or during the at-home acclimation period), because of walking with the study-provided prostheses. It is possible that a component failure or malfunction of the prostheses could cause a soft tissue injury (e.g., soreness, bruising, scrape) or other minor mechanical injury (e.g., knee or ankle joint soreness). Care will be taken to properly fit the prostheses. Only trained study staff will place and remove the guaze for trapping moisture to mimimize risk of injury. Participants will only be asked to walk on the treadmill at a speed they are comfortable with. To minimize the risk of study prostheses failure, these devices will be thoroughly tested on a benchtop and a certified prosthetist will also evaluate the quality of the prostheses prior to them being worn by participants. Additionally, most of the prosthetic componentry are commonly used, commercially-available devices. Participants will be instructed to exhibit caution while acclimating to walking with a new or modified prosthesis, and they will be asked to check their skin for redness and/or skin irritation twice a day during the daily use periods. If skin issues arise participants will be instructed to contact study staff. These are the same instructions provided when a patient receives a new or different prosthesis as part of a clinical prescription. Since participants will have a chance to wear each of the study prostheses prior to wearing them home, we do not expect any problems to arise during the two-week at-home portion of the study. Participants will be asked to contact us immediately in the event of any study-related pain or injuries to schedule an examination.

Participants could get overly hot and tired from walking in the heated room. Although unlikely, this could cause them to faint or to have a cardiac event. Participants will be asked to not consume caffeine, tobacco, and alcohol for two hours prior to each visit. They will also be instructed to drink 8-15 ounces of water prior to each visit involving walking in the hot climate-controlled space. Participants will also be encouraged to drink water as desired during the testing to stay hydrated. Handrails and a chair will be present. The Framingham Heart Risk screening will exclude individuals with risk factors for a cardiac event. Heart rate (beats per minute) will be tracked throughout the treadmill walks. For participants who do not take a beta-blocker medication (self-report), we will stop the test if their heart rate exceeds 75% of their age-adjusted maximum heart rate (220 minus age in years) for 3 consecutive minutes. For participants who do take a beta-blocker medication, we will stop the test if their heart rate exceeds 110 beats per minute for 3 consecutive minutes.

Participants may feel fatigued during or shortly after the study visits. It is possible that participants may experience some emotional or physical stress while adapting to wearing an unfamiliar prosthesis. Participants will be instructed to inform us if they feel dizziness, pain, or discomfort during the procedures and we will stop the activities to address any reported issues as needed.

Subjects may have razor burn and some embarrassment as their hair grows out from the areas shaved for the skin health tests.

The waterproof covering used to seal the gauze for perspiration collection may cause mild skin discomfort or irritation while worn or when removed (feels similar to removing a band-aid).

It is also possible that participants may experience stress or inconvenience by coming to the VA for multiple visits. Participants are free to withdraw from the study at any time.

The PI will ensure the study procedures are being properly followed by keeping the research staff well informed of the current study procedures through regular/ongoing contact. Although an injurious fall or a prosthetic component failure related to this protocol is unlikely, we will tabulate a list of any such reports that occur during the study and compare it with corresponding data available in the literature. This will allow us to analyze how much of an increased risk was due to the administered protocol. After each report of an AE, SAE or an unanticipated problem, we will evaluate study procedures for previously-assessed risks, and will determine whether any changes to the protocol are necessary to minimize risks. The use of any procedures or equipment determined to be problematicwill be suspended until these changes have been fully implemented and approved by the IRB.

Privacy and Confidentiality

See section 7.0 below for Information Security, Privacy, and Confidentality related procedures.

5.7 Data Analysis

Data collected from the laboratory-based experiments will be used to test three hypotheses. The distance that the proximal border of the liner moved from its pre- to post-treadmill walk in the environmental chamber position (marked on the skin) will be compared and enable us to test hypothesis: ($H_{1.1}$) *The amount of slippage (loss of adherence) will be different between the three prosthetic systems.* The tare weight (wet – dry conditions) of perspiration expelled from Uniprox and DAE-RED prostheses will be compared and enable us to test hypothesis: ($H_{1.2}$) *The amount of perspiration expelled will be different between the Uniprox and DAE-RED.*

Data collected from the field-based experiments will be used to test three hypotheses. The mean result from the three measures of skin hydration from the posterior compartment of the residual limb will be compared and enable us to test hypothesis ($H_{2.1}$) *Residual limb skin hydration will be different between the three prosthetic systems.* The mean result from the three measures of transepidermal water loss from the posterior compartment of the residual limb will be compared and enable us to test hypothesis ($H_{2.2}$) *Residual limb transepidermal water loss will be different between the three prosthetic systems.* The Socket Comfort Score will be used to access the comfort of the three prosthetic systems and enable us to test hypothesis ($H_{2.3}$) *The Socket Comfort Score will be different between the three prosthetic systems.*

The statistical analysis to test these hypotheses will require six linear mixed effects regression analyses. These analyses will test for differences by prosthetic system (as-prescribed, Uniprox, DAE-RED) with random effects for subject and subject by prosthetic system interaction. The experiment-wise significance will be set a priori at an alpha level of $p<0.05$ and a Bonferroni adjustment will be applied for multiple comparisons. All analyses will be performed using existing software (R Foundation for Statistical Computing with Ime4 and multcomp packages, Vienna, Austria). Exact p-values will be reported for each test.

Statistical Power Analysis

We conducted several power analyses to explore the statistical strength of our study design and estimate the number of subjects necessary to obtain meaningful results.

The first exploratory analysis uses liner slippage ($H_{1.1}$) as the metric of interest. In our current study, we fit participants with a modified PTB socket and two study prostheses: (1) a distal PIN locking liner and (2) a battery-powered dynamic air exchange (DAE) system. Subjects walked at their self-selected speed on a treadmill in our environmental chamber set to varying temperatures, including one condition at 35° C and 50% relative humidity. Liner slippage (n=10, interim results) was measured by marking the skin at the proximal border of the liner prior to the protocol and measuring the distance (mm) between the mark and the liner at the end of the protocol. Liner slippage was 23.6 ± 18.2 mm and 11.7 ± 20.0 mm while wearing the PIN and DAE systems, respectively. If we assume liner slippage while wearing the DAE-RED will be the same as the DAE, a reasonable assumption as the body-weight activated pump in DAE-RED generates the same vacuum levels with active subjects as the battery-powered pump in the DAE, then we calculate a 99 percent probably that the study will detect a difference between prostheses at $p<0.05$ with *10 subjects*.

A second exploratory power analysis for the skin hydration ($H_{2.1}$) metric was performed using published values from Firooz [36]. Using the same instrument (Corneometer CM825; Courage & Khazaka, Köln, GER) proposed in our study, Firooz measured skin hydration of subjects diagnosed with atopic dermatitis (n=30) and age-matched controls (n=30) at several upper body sites including the dorsal surface of the hand. Atopic dermatitis is a chronic, reoccurring, pruritic form of dermatitis prone to dry skin and other complications. Firooz found skin hydration of 38.9 ± 12.8 and 29.6 ± 10.0 (arbitrary units) for the control group and atopic dermatitis group, respectively. While Firooz's study used a between-subject experimental design, our proposed within-subject study can be expected to have less variance. If we assume a standard deviation of 12.8 for the difference between study prosthetic systems and a difference between means of 9.3, there is an 80% probability to find a significance difference between prosthetic systems with *17 subjects*. Choi [37] also used the same instrument to measure skin hydration, but at eight different anatomical sites including the leg posterior surface, on children with extrinsic atopic dermatitis (n=41) and age-matched controls (n=8). Choi found skin hydration of 64.8 ± 14.4 and 52.1 ± 14.2 (arbitrary units) for the control group and atopic dermatitis group, respectively. Choi also used a between-subject experimental design which

would likely have greater variance than our proposed within subject experimental design. Assuming a standard deviation of 14.4 for the difference between study prosthetic systems and a difference between means of 12.7, there is an 96% probability to find a significance difference between prosthetic systems with *20 subjects*.

A third exploratory power analysis for the transepidermal water loss ($H_{2.2}$) metric was performed, also using results reported by Choi [37]. Using the same instrument (Tewameter TM300; Courage & Khazaka, Köln, GER) proposed in our study, Choi measured transepidermal water loss as described above and found the transepidermal water loss of 16.5 ± 8.17 and 28.8 ± 18.8 g/m^2/h for the controls and extrinsic atopic dermatitis children, respectively. If we assume a standard deviation of 13.0 for the difference between study prosthetic systems and a difference between means of 12.3, there is an 97% probability to find a significance difference between prosthetic systems with *20 subjects*. We note Choi reported a large difference in variances between groups (8.17 and 18.8 g/m^2/h), and the power analysis is particularly sensitive to different variances. We used a value mid-way between the two groups; using a greater variance of 18.8 results in a 79% probability to find a difference with *20 subjects* while using a smaller variance of 8.17 results in a 99% probability to find a difference with *20 subjects.*

These analyses provide confidence that our proposed within-subject experimental design will provide meaningful results with a sample population of 20 subjects.

Supplemental Measures

Absorbent pads placed on the skin of the contralateral limb during the laboratory protocol will be used as a control measure of perspiration. The tar weight of the pad will be used to calculate the perspiration rate by dividing the weight of the pad by its surface area and the donned duration, expressed in grams per meter square of body surface area per hour (g m^{-2} h^{-1}). We will perform a linear mixed effects regression analysis on these samples to determine if there were differences in perspiration rate across study prosthetic systems (independent variable). If a significant difference is found, we will perform an analysis of co-variance in consultation with our Center's biostatistician to quantify the effects on the study results.

The number of prosthetic steps taken over the two-week field protocol will be used as a control measure of activity and to verify participants are wearing the study prostheses. After wearing each study prosthesis in their home, work, and community environments while participating in their usual daily activities, the Fitbit Zip will be removed from the prosthetic pylon and synchronized with the Fitbit Dashboard. The prosthetic steps taken over the two-week period will be summed and compared. We will perform a linear mixed effects regression analysis on this data to determine if there were differences in activity across study prosthetic systems (independent variable). If a significant difference is found, we will perform an analysis of co-variance in consultation with our Center's biostatistician to quantify the effects on the study results.

5.8 Withdrawal of Subjects

This is not a treatment study; withdrawing or being terminated from this study will not have an impact on participant safety. A study clinician or the PI may withdraw a participant without their consent if he or she feels that it is not in a participant's best interest to continue in the study or the person is unable to complete the study procedures. All data previously collected from participants who withdraw or are withdrawn will be kept and may be used in the study data analysis. Participants may withdraw at any time by informing the Research Coordinator and/or the PI. If a participant wants to withdraw or we choose to withdraw a participant, while she/he are using study equipment (i.e., one of the prostheses) we will arrange for the study prosthesis to be returned/removed and the participant's as-prescribed prosthesis to be re-fit.

6. Reporting

All safety information on AEs, SAEs, unanticipated events or problems, and protocol deviations will be collected. This information will be collected at study visits and whenever subjects call to report a problem. The information will be collected on VA IRB forms (Report of a SAE and/or Problem Form, or Report of Problems (ROP) Form) and in AE log forms as needed. Safety data will be collected on an as-needed basis and will begin upon enrollment into the study. All safety reporting requirements will be followed. Any anticipated AEs will be recorded on a log sheet and reported annually with the CRQ.

If we become aware of relevant findings or information that may affect subjects' health or welfare, we will contact subjects by phone and/or a letter to notify them.

Additional Safety Monitoring

Dr. Bruce Sangeorzan (VA Puget Sound), will act as the Medical Monitor for this study. After each report of a SAE or problem, the Medical Monitor will evaluate study procedures for previously-assessed risks and will determine whether any changes must be made to minimize risks. The Medical Monitor has the authority to stop the research protocol in progress, remove individual participants from the research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB assesses SAEs or other reports. As noted above, cumulative safety data will be reviewed yearly by the PI and the Medical Monitor and will be reported to the IRB in the Continuing Review Questionnaire (CRQ). The Medical Monitor will periodically (quarterly) have discussions with the PI about the research progress to date. The Medical Monitor will periodically (quarterly) review study enrollment, data, and procedures. The PI and the Medical Monitor will ensure security, privacy, and confidentiality by following all IRB-approved procedures. The Medical Monitor will review all unanticipated problems involving risk to subjects or others, serious adverse events and all subject deaths associated with the protocol and provide an unbiased written report of the event to the IRB. The Medical Monitor will comment on the outcomes of SAE events or problems and in the case of a serious adverse event or death, he will comment on the relationship to participation in the study. The Medical Monitor must also indicate whether he concurs with the

details of the report provided by the principal investigator. Reports for events determined by either the investigator or Medical Monitor to be possibly or definitely related to participation and reports of events resulting in death will be promptly forwarded to the CDMRP and the ORP HRPO.

7. Information Security, Privacy, and Confidentiality

As with any study, it is possible, although unlikely given the impersonal nature of the data collected, that participants may experience a loss or invasion of privacy or confidentiality because of participation in this study. The risk of harm is minimal and the protections described here will be followed.

Electronic data with PHI/sensitive information will be stored on the secure server at the VA Puget Sound. These data will only be accessed by authorized study personnel. Hardcopies of VA sensitive data and documents with PHI will be stored in a locked file cabinet in a locked office at the VA Puget Sound (Seattle). Study files/data with PHI or sensitive information will not be sent off-site. This is a locked facility to which only study investigators have access. Identifiable data will not be transmitted, transported, or stored on portable media or laptops outside of the VA, and the data will only be accessed by authorized VA study staff. We will notify the Information Security Officer of the location of the hardcopy data/files via the Data Inventory form. If study data is improperly used or disclosed we will notify the ISO and Privacy Officer within one hour of becoming aware of the issue.

Study staff will only have access to the minimum necessary identifiable information needed to perform their role. Study staff that depart the VA or are removed from the research team will be promptly removed from the research application and will no longer have access to sensitive study data.

Study data will be labeled with a study assinged code and de-identified data sets will be created/used when data is made publicly available and transmitted without restriction. A copy of de-identified data will also be made available to public search, retrieval, and analysis per the limitations the Data Management Access Plan (DMAP). The key to the code will be stored separately from the study data, and only designated VA study staff will have access to it.

The Fitbit Zip step counter and web-based app will be used to collect de-identified step count data. Researchers will set up study accounts for the application (e.g., user ID: Copatwo Studyone, copa2study1@gmail.com), and study participants will not interact with the application. No PHI/PII will be entered when the study accounts are created. Study staff will sync the Fitbits when participants come to the VA for study visits and will pull the data from the Fitbit website. They study IDs will be securely stored in the crosswalk at the VA.

De-identified, non-sensitive electronic data labeled with the study assigned codes, and all 18 HIPAA identifiers removed or converted to de-identified format, may be stored on password-protected equipment (computers/laptops/SD cards) but will not be encrypted. De-identified data files may be

sent off-site via email, file transfer software, and/or other electronic media (CD/DVD, USB drive) to our biostatistician (Jane Shofer, MS), off-site collaborator (Charles King, CP), and between study investigators. Arusha Control, Inc. (off-site collaborator) will only have access to de-identified data.

Any consented photography or video will protect participatnts' identity (e.g., by obscuring the subject's face and any identifying marks like tattoos). The videos and photos may include the participant's entire body, but they will be anonymized during data processing; the participant's face will be blurred, any identifying marks will be covered or blurred, and then the original file will be deleted. If a participant's voice is accidently recorded, that section of video would be altered prior to any use outside of the VA study team. The video camera and the recording media (e.g., SD cards, optical disks) will be stored in a locked office at the VA Puget Sound. Photos and videos that do not contain identifiable information may also be stored on password-protected computers for future use in scientific presentations and publications. Study records with PHI/PII will be stored until the end of the study, and for a minimum of 6 years after the study is completed (in accordance with the records retention schedule); they will be destroyed using VA approved procedures. Hard copy data with identifiable and/or sensitive information will be shredded per VA approved policies. Electronic data containing identifiable information will be wiped using VA approved software. De-identified data will be stored indefinitely.

VA medical records will be created, or updated, for each participant. The medical record will include information about enrollment in this study, cholestrol test results (if done at VA), and information about any other medical treatment received (if needed) that is related to this study. All authorized users of the national VA medical records system can have access to the medical record. This may include health insurance companies who are being billed for medical costs. This record will be kept forever.

8. Communication Plan

This is not a multi-site study. If students or staff at the University of Washington are participating as study staff at the VA, the PI will assure that the appropriate approval is obtained from the UW Human Subjects Division.

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