Title: Lower limb prostheses for individuals who carry infants, toddlers, and other loads.

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Human Subjects Protocol

VA Puget Sound IRB

Lower Limb Prostheses for Individuals Who Carry Infants, Toddlers, and Other Loads

MIRB # 01799

Funding Agency: Department of Veterans Affairs, Rehabilitation Research and Development Service

Principal Investigator: Glenn Klute, PhD

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Abstract

The natural lower limbs provide important biomechanical functions such as body weight support, forward propulsion, and balance control during ambulation. When the loads borne by the lower limbs change, lower limb muscle activation responds accordingly to enable seamless continuation of biomechanical function. These loads can change suddenly, such as when carrying an infant, toddler, or other load like a heavy backpack. For individuals with a lower limb amputation, these sudden changes to weight-bearing loads can be problematic because they can negatively impact walking performance. One reason walking performance may suffer is that the properties of most prosthetic limbs, such as their stiffness, are constant and do not change to suit varying load conditions. Another reason is that the most widely prescribed prosthetic feet do not have motors, sensors, or brain-like controllers that act to replace the neuromuscular system of the amputated limb. Regardless of the reason, no evidence exists to guide prescription practice for veterans who walk with a prosthesis and experience sudden load changes.

The aim of this research is to create guidance for VA clinicians who prescribe prostheses to veterans with a lower limb amputation who frequently carry infants, toddlers or other loads. To achieve this aim, we will conduct a human subject experiment with help of twenty individuals with below-knee amputations. Study participants will walk on a treadmill with no added load and four added load conditions using a weighted pack (13.6 kg or ~30 lbs) to simulate an infant, toddler, or other load. The four conditions include the pack strapped to their front, their back, and carried with their arms on the intact limb side and the prosthetic limb side. Each participant will wear a usual prosthetic foot, this same foot with a heel-stiffening wedge, the same prosthetic foot but one category stiffness higher, a new-to-market dual keel prosthetic foot intended for load carrying situations, and a powered ankle foot prosthesis. We will analyze the results of this experiment to determine which prosthetic foot (if any) and which load carrying condition (if any) is most advantageous.

List of Abbreviations

AE – adverse event
ANOVA – analysis of variance
ASIS - anterior superior iliac spine
CCTV - closed circuit television
CO - Colorado
CRQ – continuing review questionnaire
d – Cohen's *d* statistic
EMG – electromyography
GAS - medial gastrocnemius
GMAS - gluteus maximus
GMED - gluteus medius
GRF – ground reaction force
H – hypothesis
HAM - biceps femoris long head
HIPAA – health insurance portability and accountability act
IRB – institutional review board
ISO - Information Security Officer
Kg - kilograms
Lbs - pounds
M - Million
MA – Massachusetts
MD – Maryland
MIRB – Minneapolis Institutional Review Board
N - number of individuals
PHI – personal health identifiers
PI – principal investigator
PO – privacy officer
RF - rectus femoris
ROP – report of other problem
SA – specific aim
SAE – serious adverse event
SOL – soleus
SSWS - self-selected walking speed
TA - tibialis anterior
UW – University of Washington
VA – Veterans Affairs
VAPSHCS – Veterans Affairs Puget Sound Health Care SystemVAS - vastus medialis
WA - Washington

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Protocol Title: Load Carriage by Individuals with Lower Limb Amputation

1.0 Study Personnel

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2.0 Introduction

Prosthetic feet help facilitate a more natural gait by attempting to emulate the biomechanical functions normally provided by the anatomical foot and ankle such as body support, forward propulsion and balance control. Clinicians select prosthetic feet based on the patient's body weight and self-reported activity level. A heavier, and/or more active individual, is prescribed a stiffer prosthetic foot. Manufacturers offer products with a range of stiffnesses that are demarcated by as many as nine ordinal categories. Each category is intended to suit a somewhat narrow weight range, typically spanning ~10 kg (~22 lbs) at an activity level defined as low, moderate or high impact. Changes in body weight can precipitate a change in the prescribed stiffness category, but body weight changes occur slowly and needed changes are usually addressed on an annual basis.

Changes to the load applied to a prosthesis can also happen quickly, such as when an individual carries an infant, toddler or other heavy item. Infants, who are unable to mobilize independently, have a mean mass of ~6.5 kg, while toddlers, who are able to mobilize independently, exhibit a range from 11.5 to 19.7 kg [1]. Women carry children more often than men [2], but men are more likely to carry older children [3]. Children and objects can be carried in different ways [4][5], but the most common methods include posteriorly in a backpack, anteriorly in a sling or with arms, or asymmetrically with arms on either side (see Fig. 1). Carrying loads in general cause an increase in oxygen consumption [6], but loads carried posteriorly are less metabolically costly [7]. However, American children are most often carried on the front [8]. Side carrying is less common [8], but allows more accessible interaction between the child and parent [3]. While non-human primates infants use their grip to assist with carriage, human parents get little to no help from their infants [3].

Carrying loads is a frequent part of many jobs. Civilian workers spend almost 4.5 hours per workday standing or walking and the mean maximum weight lifted or carried in their jobs is about

16 kg [9]. Approximately 14% of all civilian jobs had a strength level of “heavy work”, defined as occasionally carrying 23 to 45 kg, frequently carrying 12 to 23 kg, or constantly carrying items of 4.5 to 11 kg or less [10]. Among occupations, heavy work accounted for 46% of jobs in construction and extraction, 35% of jobs in installation, maintenance, and repair, 32% of jobs in transportation and material moving, and 22% of jobs in healthcare support [10]. Fully 45% of civilian jobs had a “medium work” level, defined as occasionally carrying 10 to 23 kg, frequently carrying 5 to 11 kg, or constantly carrying items of 5 kg or less [10].

Not surprisingly, individuals with lower limb amputations respond to load carriage conditions with greater metabolic costs [11] and asymmetric biomechanical deviations such as increased intact limb joint power generation and absorption and greater dorsiflexion of their prosthetic foot in late stance [12]–[14]. As discussed in the recent work by Koehler-McNicholas [15], this greater dorsiflexion of prosthetic feet is in stark contrast to the unaltered kinematics of the ankle-foot motion in non-amputees and suggests a significant short-coming in these devices. During added load conditions, a prosthetic foot with greater stiffness would be clearly desirable [16], but this benefit would be offset in the no load condition because the energy storage and release function, which facilitates locomotion, is reduced [17].

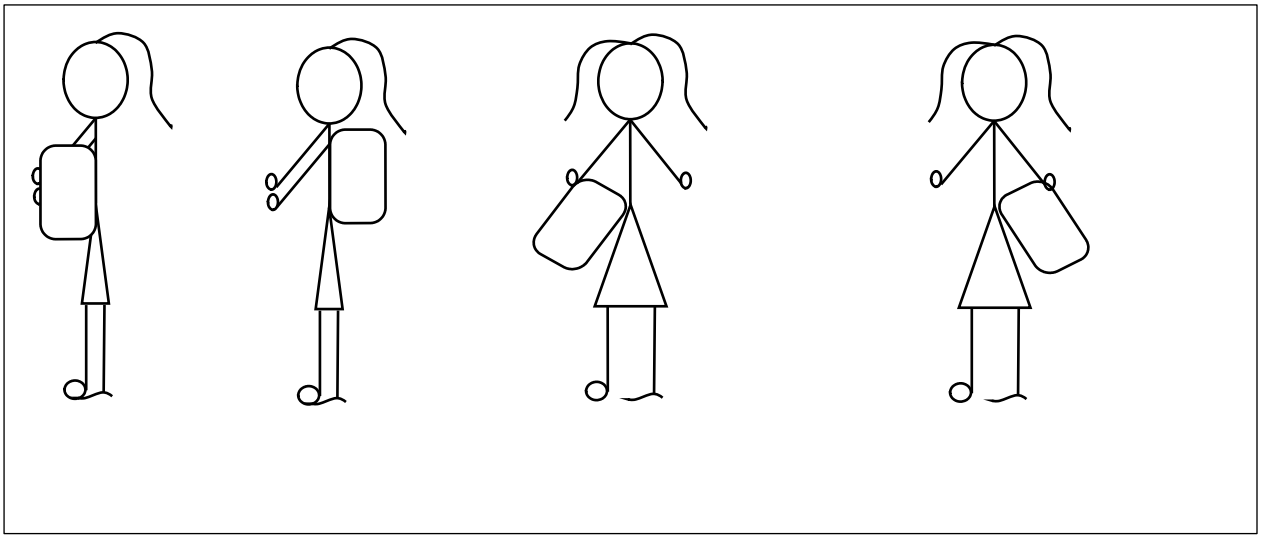

Fig. 1: Load carriage techniques.

While the biomechanical deviations depend on load magnitude and carriage technique, the negative consequence of load carriage include injuries such as foot blisters, pain and inflammation of the foot, knee and back, and stress fractures [5]. Individuals with vulnerable limbs due to trauma or diabetic/dysvascular etiologies are hypothesized to be at even greater risk for these common injuries.

For individuals with lower limb amputations who routinely carry loads using techniques (see Fig. 1), clinicians have several low-cost options including the prescription of a stiffer category foot, the addition of a heel wedge to stiffen the heel, or the prescription of a dual keel prosthetic foot (see Fig. 2). The dual keel prosthetic foot has a full-length primary keel and a truncated secondary keel. As additional loads are applied, the primary keel engages the secondary keel such that the prosthetic foot becomes stiffer. Aside from some weighted walking tests (n=3) with the dual keel prosthesis, where a weighted vest placed the additional load near the body’s center of mass such that the resulting biomechanical gait deviations were, little evidence exists to support these prescription practices.


Fig. 2: Study prosthetic feet: Vari-Flex Low Profile (Össur), Vari-Flex Low Profile with 6.8° heel-stiffening wedge (shown in blue), Thrive dual keel (Freedom Innovations).

A more expensive prescription option is a commercially available  powered ankle-foot (Empower, Otto Bock, Austin, TX). The clinical value of this device is an open question with some research suggesting a benefit (e.g., [18][19][20]) and other research suggesting mixed results (e.g., [21][22][23][24]). Efficiency (laboratory testing) and efficacy (real world testing) during load carriage has yet to be demonstrated.

The target population of this research are veterans with lower limb amputation. In 2002, 82,000 Americans had a lower limb amputation arising from complications associated with diabetes [25]. The direct U.S. hospital costs related to these procedures could be conservatively estimated to exceed $350M annually [26]. Available data suggests the VA performs between 3,000 and 5,000 lower limb amputation surgeries on veterans of diabetic and dysvascular etiology each year [27] [28]. These veterans are among the 623,000 Americans who live with a major lower limb amputation [29], a population whose growth due to diabetes doubled between 1990 and 2008, but has since fortunately plateaued [30] 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=1,795 major limb amputation (all causes) from 2000 to 2011 [31]; n=1,645 major limb amputation (battle injuries) from 2001 to 2015 [32]). These individuals tend to have few comorbidities and may be expected to rely on the VA for their rehabilitative care for many years to come.

This research will not specifically target vulnerable populations for enrollment.

3.0 Objectives

The purpose of this research is to provide prosthesis prescription guidance for VA clinicians whose patients carry infants, toddlers, and other loads.

The specific aim of this research is to identify the study prosthetic foot that minimizes biomechanical gait deviations when compared to the standard-of-care for veterans with lower limb amputation who carry infants, toddlers, or other loads.

We will conduct a human subject experiment with unilateral transtibial amputees (n=40). Each participant will walk on an instrumented treadmill with no added load and four added load conditions of 13.6 kg: anterior, posterior, intact-side carry, and prosthetic-side carry. Using a

within-subject experimental design with block randomization, each participant will wear: a standard-of-care prosthetic foot, this same prosthetic foot with a heel-stiffening wedge, this same prosthetic foot but one category stiffer, a dual keel prosthetic foot intended for load carriage applications, and a powered ankle-foot purported to adapt to changing loads.

In general, we hypothesize that one of these prosthetic feet will minimize biomechanical deviations for (1) no added load, (2) anterior added load, (3) posterior added load, (4) intact-side carry load, and (5) prosthetic-side carry load.

Our specific hypotheses for each load condition are:

H1 a study prosthesis exists that maximizes the vertical GRF impulse (a measure of body support),

H2 a study prosthesis exists that maximizes the anterior GRF impulse (a measure of body forward propulsion),

H3 a study prosthesis exists that minimizes the peak-to-peak range of sagittal plane whole-body angular momentum (a measure of balance control primarily for anterior and posterior added load conditions),

H4 a study prosthesis exists that minimizes the peak-to-peak range of frontal plane whole-body angular momentum (a measure of balance control primarily for intact-side and prosthetic-side added load conditions), and

H5 a study prosthesis exists that minimizes the mechanical energy expenditure (allow for more efficient locomotion).

4.0 Resources and Personnel

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

Under the supervision of the PI, 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 is responsible for IRB related matters.

There are no contractors involved in the data collection procedures for this study.

There are no Data Use Agreements entered into for this study.

5.0 Study Procedures

5.1 Study Design

This study will employ a within-subject experimental design. Each participant will wear, in block randomized order, a standard-of-care prosthetic foot, this same prosthetic foot with a heel-stiffening wedge, this same prosthetic foot but one category stiffer, a dual keel prosthetic foot

intended for load carriage applications, and a powered ankle-foot purported to adapt to changing loads. All study prostheses are commercially available. Each participant, wearing each of the study prostheses, will walk on an instrumented treadmill with no added load and four added load conditions of 13.6 kg: anterior, posterior, intact-side carry, and prosthetic-side carry. The load condition will be presented in block randomized order. The protocol consists of two study visits of no longer than four hours each. A third visit may be needed if data are found to be missing or corrupted, also lasting no longer than four hours.

The anticipated risks of the study include injury to the residual limb (skin irritation or damage) while participating due to wearing the study prostheses (which may be heavier than their as-prescribed prosthesis) or carrying study loads (13.6 kg). Our research prosthetist will discuss any concerns such as low back pain or arthritic joint problems with each participant to determine study suitability and minimize this risk. Some study participants of diabetic/dysvascular etiology may be at risk of injury to the contralateral limb due to carrying study loads. Our research prosthetist will discuss these issues with each participant to establish study suitability. Individual participants in the proposed research are not expected to receive a direct benefit from their participation. The potential benefit of the proposed research is to the veteran lower limb amputee population in general. The anticipated benefit is knowledge of how heel-stiffening wedges, stiffer feet, dual keel prostheses, and powered prosthesis function under varying load conditions. The risks to subjects are low; no life sustaining or life supporting interventions are used as a part of the proposed research protocol. The potential benefit and low risk suggest a favorable risk/benefit ratio.

Individuals with lower limb amputation may also be at a slight risk of injury (e.g., arising from a trip, a fall, or failure of the study prosthesis) or discomfort while they wear the study prostheses. The study prosthesis may have properties that are different than their as-prescribed prosthesis. As per clinical practice, subjects will be instructed to exhibit caution while acclimating to the study prosthesis. This is the same instruction provided when a veteran receives a new prosthetic component as part of a clinical prescription. Subjects will be asked to contact the PI or study staff in the event of any study-related pain or injuries to schedule an examination

The study population will be individuals with unilateral transtibial amputations. We anticipate approaching up to 500 individuals to enroll up to 40 individuals.

Vulnerable populations will not be specifically targeted for enrollment.

This study will not include specimen banking.

5.2 Recruitment Methods

Up to 500 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.

Recruitment Activities at the VA

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

Designated research staff will screen relevant clinic lists in the VA and UW electronic medical record systems (orthopedics, podiatry, orthotics and prosthetics, amputee clinic) to identify potential participants.

After review of relevant clinic lists, 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 the electronic medical record system 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 the electronic medical record systems to identify individuals who may meet inclusion and exclusion criteria and mail them the approach letter.

If potential participants have not spoken with us between 7 and 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 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.

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 the electronic medical record system 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 Loss Prevention and Prosthetic Engineering 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.

Recruitment Activities in the Community

Clinician Referral

Designated VA staff will send providers working in relevant clinics around the community a clinician approach letter and/or email explaining the nature of the research our Center conducts. If interested, designated study staff will inform providers about specific studies currently recruiting and inclusion/exclusion criteria so they can refer potential participants to contact the study team. Flyers/brochures may be provided to clinicians to give to patients interested in the

study. Clinicians may also provide us (via in-person/on the phone) with the names and contact information of patients they are aware of who may be a good fit for the study, and we will send an approach letter. Designated staff may visit clinics periodically to replenish flyer/brochure supplies and educate clinicians on new studies.

Support Groups

Designated VA staff will send support group leaders an approach email explaining the nature of the research our Center conducts. If interested, designated staff will attend support groups to see if patients are interested in participating in our research. We will give interested patients more information about the study. We will bring flyers/brochures to hand out to interested patients.

Payment to Subjects

Subjects will receive $50/hour for the first hour of each study visit, then $30/hour for the rest of each study visit to the VAPSHCS. For subjects traveling 20+ miles one way for appointments (40+ miles total), we will provide compensated mileage rates in accordance with the Veterans Affairs Beneficiary Travel program. This amount may fluctuate. To ensure accuracy, study staff will check to make sure the most up-to-date amount is being used prior to adding travel compensation to total compensation amount. Current mileage rates can be found at https://www.va.gov/HEALTHBENEFITS/vtp/beneficiary_travel.asp. For subjects traveling via ferry for appointments, we will provide full ferry fare compensation. We will not offer compensation for other individuals traveling to the appointment with the participant. To ensure the most up-to-date fares are used, study staff will check the Washington State Department of Transportation ferry fare website (https://www.wsdot.wa.gov/ferries/fares/) prior to adding ferry fare compensation to total compensation amount. We will determine if travel compensation is required based on contact information recorded during enrollment. If we determine that a participant is not a good fit for the study and cannot do the procedures, s/he will still be compensated for the first hour of the visit and any applicable travel compensation. Payments will be dispersed in cash or by check; checks will be mailed about 6-8 weeks after the final visit.

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. Unilateral transtibial amputee
2. Age 18-70
3. Have been fitted with and used a prosthesis for at least six months
4. Do not use heel stiffening wedges or bumpers in their as-prescribed prosthesis
5. Wear their prosthesis for at least four hours per day
6. Are moderately active by self-report

7. Can be fitted with the study prostheses (prosthetic foot size, stiffness category and build heights)

Exclusion Criteria:

1. Do not have a proper fit and suspension and one cannot be achieved with clinical resources
2. Presence of disorder, pain, or injury other than amputation that interferes with gait

5.5 Study Evaluations

Study Prostheses

Each participant will be fit with four different prostheses: (1) a standard-of-care prosthetic foot, (2) this same prosthetic foot with a heel-stiffening wedge, (3) a dual keel prosthetic foot intended for load carriage activities, and (4) a powered ankle-foot purported to adapt to changing loads. For the standard-of-care prosthetic foot, we will use the Sierra prosthetic foot (Freedom Innovations, Irvine, CA). This prosthetic foot is available in sizes 22 to 31 cm (most VAPSHCS prescriptions are from size 27 to 29 cm), stiffness categories 1 to 9 (most VAPSHCS prescriptions are categories 5, 6, or 7). For adjustment of heel stiffness and roll-over characteristics, the Sierra prosthetic foot comes standard with an optional heel wedge that, when affixed to the heel keel as directed, results in a one category increase in stiffness of the heel keel. We also will use the only commercially available dual keel foot, the Thrive (Freedom Innovations, Irvine, CA). This prosthetic foot is available in sizes 22 to 31 cm and stiffness categories 1 to 9 (note: the stiffness categories of the Sierra and Thrive prosthetic feet are identical). For the powered ankle-foot, we will use the only commercially available powered ankle-foot, the Empower (Otto Bock, Austin, TX). This prosthetic ankle-foot is available with a foot keel in sizes 25 to 30 cm and three body-weight dependent stiffness categories.

Load Carriage

To add anterior and posterior loads, subjects will don a weighted and padded pack fitted with additional straps to secure it to the torso (Classic; Camelbak, Petaluma, CA). The pack will have weights placed inside it so that the total mass is 13.6 kg. To allow the participant to carry the load on the intact- and prosthetic-sides of their torso with their arms, the straps from the padded backpack will be removed or constrained.

Experimental Protocol

The protocol consists of two study visits. A third visit may be needed if data are found to be missing or corrupted from previous study visits. At the first visit, subjects will be screened for inclusion and exclusion criteria and consented. Next, each subject will be asked to walk at their own pace 20 m down a straight hallway while wearing their as-prescribed prosthesis. An average of three trials will be used as a measure of their self-selected walking speed (SSWS). We will also collect subject height, body mass, age, components used in as-prescribed prosthesis, years since amputation, amputation etiology, race, ethnicity, and sex/gender.

The study prostheses will then be fit, in random order, to each participant and aligned by a licensed and certified prosthetist (GE Kaufman, L/CPO) using standard clinical procedures. We will use a sock and foot cover to blind the participants to the study prostheses when possible (use of the powered ankle-foot will be obvious). Participants will continue to use their existing socket and suspension system, but pylon length will be adjusted as needed to accommodate the study prostheses' build height. Subjects will then be provided with at least 15 minutes to walk

about with no added load and the added load conditions to learn how each study prosthesis performs and feels. Rest breaks will be provided as needed. After the subjects have worn all four study prostheses for all load conditions, the subjects will then don their as-prescribed prosthesis. This will complete the first study visit.

After at least one overnight rest period, we will ask the subjects to return to the laboratory for the second study visit. Subjects will be asked to don body fitting garments, after which sixty-two 14 mm reflective markers will be placed on each subject in locations consistent with a modified version of Vicon's Plug-in-Gait full-body model (Centennial, CO). Anthropometric measures will be recorded for static and dynamic modeling. The Plug-In Gait model will be modified by adding reflective markers at the medial malleolus, medial elbow, and first and fifth metatarsal heads of the feet. The thigh and upper arm segments will be tracked with marker clusters instead of wands. The shank segments will be tracked with markers placed on the fibular head and tibial tuberosity instead of tibial wands. Hip joint centers will be calculated using regression equations based on the inter-ASIS distance of the pelvis.

To help understand how individuals achieve biomechanical performance deviations, we will collect surface EMG data from the primary muscle groups involved in human walking. Specifically, we will shave the skin of the tibialis anterior (TA), medial gastrocnemius (GAS), soleus (SOL), vastus medialis (VAS), rectus femoris (RF), biceps femoris long head (HAM), gluteus medius (GMED), and gluteus maximus (GMAX) of the intact leg along the muscle line of action between the origin and insertion points, and clean it with alcohol to decrease impedance. For the residual limb, we will do the same for the VAS, RF, HAM, GMED, and GMAX. Disposable dual surface EMG electrodes with 2.0-cm spacing will then be applied and connected with a pinch-style terminal to a sensor probe (Noraxon, Inc.) with reference electrode and preamplifier. Each electrode will be held securely in place with Coban (3M, Inc.). Data from the probes will be wirelessly transmitted to a receiver where the data will be processed, synced, and stored in real-time with our existing motion capture system (Vicon, Centennial, CO).

Using the same methods as the first study visit, subjects will be blinded to and fit with each study prosthetic foot in random order. After the first study prosthesis is fit, subjects will walk on our existing instrumented treadmill (AMTI, Watertown, MA) their SSWS determined during the first study visit. In random order, subjects will be asked to walk for one minute with no load and the four added load conditions. Kinematic and kinetic biomechanical data will be collected during each one-minute trial using a 12-camera Vicon system (Vicon, Centennial, CO) and two force plates embedded in the split-belt treadmill. Rest breaks will be provided as needed. After each load condition, we will ask the subject to rate their satisfaction with the functional performance of the study prosthesis using an 11-point Likert scale (0-10) where 0 is defined as completely dissatisfied and 10 as completely satisfied. Subject participation in the study will conclude after they have worn all four study prostheses.

5.6 Data Analysis

Kinematic and kinetic data from the experiment will be processed in Visual 3D (C-Motion Inc., Germantown, MD) and aggregated using custom project specific software (Matlab; Mathworks, Natick, MA). To determine changes in walking performance, we will calculate biomechanical quantities related to body support, forward propulsion and balance control including: the vertical ground reaction force (GRF) impulse, the anterior GRF impulse, and the peak-to-peak range of the frontal and sagittal whole-body angular momentum. We will also calculate mechanical energy expenditure (i.e., the sum of the joint mechanical work of each leg). The GRF and joint work metrics will be normalized by body weight and added load while whole-body angular momentum will be normalized by body weight and added load, walking speed and leg length.

Linear mixed-effects regressions will be used to detect differences in the biomechanical quantities (dependent variables) between study prostheses (independent variables) for each load condition separately (anterior, posterior, intact-side carry, and prosthetic-side carry) following an assessment of normality. This method allows inclusion of subjects who do not complete all study procedures (repeated measures analysis of variance (ANOVA) models do not). These analyses will test for differences between the study prostheses across the four different load carriage conditions with random effects for subject and subject by study prosthesis interaction. If the data is not normally distributed, we will consult with our biostatistician on an appropriate transform. An omnibus test for significance will generated using a likelihood ratio test with an alpha level of 0.05. Individual pair-wise differences will be assessed using simultaneous inference and associated 95% confidence intervals. All statistical analyses will be performed by study staff using existing VA enterprise software (SPSS Statistics v22; IBM, Inc.). Exact p-values will be reported for each test.

We conducted an exploratory power analysis for hypothesis **H1**. For this within-subject repeated measure study design, we used recently collected data (n=1) to compare potential differences across our study prostheses. When the subject walked at their self-selected speed with 13.6 kg added posterior load, the difference in vertical GRF impulse was 27.0 N*s/kg between two study prostheses with a mean standard deviation of 18.3 N*s/kg. We calculated 99 percent power to find a significant difference between the prostheses at $p<0.05$ for 20 subjects. For the anterior added load condition, the difference in vertical GRF impulse was 16.1 N*s/kg between two study prostheses with a mean standard deviation of 16.0 N*s/kg. We calculated 85 percent power to find a significant difference between the prostheses at $p<0.05$ for 20 subjects.

We also conducted an exploratory power analysis for hypothesis **H2**. When subjects walked at their self-selected speed with 13.6 kg added posterior load, the difference in the anterior GRF impulse was 1.8 ± 1.3 N*s/kg between two study prostheses. We calculated 98 percent power to find a significant difference between the prostheses at $p<0.05$ for 20 subjects. For the anterior added load condition, the difference in the anterior GRF impulse was 4.1 ± 2.4 N*s/kg between two study prostheses. We calculated 99 percent power to find a significant difference between the prostheses at $p<0.05$ for 20 subjects.

To aid in interpreting clinical meaning, we will calculate effect size (Cohen's *d* statistic) and will consider d values of 0.2, 0.5, and 0.8 to be small, moderate, and large effect sizes, respectively [33]. We will also interpret results relative to minimal detectable change criteria, when available, to ensure our statistical findings are clinically relevant.

Secondary Analyses

The satisfaction data from the experiment will be aggregated using project specific software (Matlab; Mathworks, Natick, MA). We hypothesize that there exists a study prosthesis that maximizes satisfaction across the different load conditions. The statistical analyses to test this secondary hypothesis will require a two-factor (prosthesis, load condition) Friedman analysis of variance (ANOVA). This analysis will test for differences between the four different study prostheses across the four different load conditions. 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 statistical analyses will be performed using existing VA enterprise software (SPSS Statistics v22; IBM, Inc.). Exact p-values will be reported for each test.

Surface EMG data from the walking trials will be processed with existing custom algorithms in Matlab (Mathworks, Inc.). The collected data will be high-pass filtered (bidirectional Butterworth, 4th order, 50 Hz cutoff frequency), demeaned, and rectified, and then further smoothed using a

moving root-mean-square (RMS) window of 80-ms. Subject average RMS profiles for each muscle at each condition will be normalized to the average peak RMS value of the same muscle for each stiffness setting while walking on the 0° condition. The kinematic and kinetic data will be filtered with a 4th-order Butterworth filter with cut-off frequencies of 6 Hz and 20 Hz, respectively, using Visual3D (C-Motion, Inc.). This data will be used to support the biomechanical observations.

5.7 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 a study prosthesis, we will arrange for their as-prescribed prosthesis to be returned and fit to the participant.

6.0 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.

7.0 Privacy and Confidentiality

This study will not use or disclose Protected Health Information (PHI). No Certificate of Confidentiality will be required. 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.

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 but will not be encrypted. De-identified data files may be sent off-site via email, file transfer software, and/or other electronic media to our biostatistician, off-site collaborators, and between study investigators.

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 will be stored in a locked office at the VAPSHCS. 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.

8.0 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.

9.0 Information Security and Data Storage/Movement

Electronic data with PHI/sensitive information will be stored on the secure server at the VAPSHCS. 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 VAPSHCS. 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 (ISO) 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 assigned 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.

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 to our biostatistician (Jane Shofer, MS), off-site collaborator (Richard Neptune, PhD), and between study investigators. Off-site collaborators will only have access to de-identified data.

Study records with PHI/PII will be destroyed using VA approved procedures and in accordance with the records retention schedule after the study is completed. 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.

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