Title: Pivot-Flex Foot: Optimal Coupling Ratio Between Transverse and Sagittal-plane Motions Using a Torsionally Adaptive Prosthesis for Individuals With Lower Limb Amputation

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Human Subjects Protocol

VA Puget Sound IRB

Pivot-Flex Foot

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Abstract

Background:

The standard lower limb prosthesis is optimized for straight line walking with less focus given to rotational capabilities that facilitate movements like turning and balancing while walking. The natural ankle and foot have a complex set of joints that allow for paired turning and flexing motions important during walking; the ankle and foot work together to turn/twist horizontally (relative to the leg) while also flexing forward and backward (landing and pushing off the ground). The rotational flexibility of the natural foot and ankle help manage the twisting forces generated during walking but this function has not been replicated in prosthetic feet and ankles. This limitation causes twisting forces from turning movements to be sent to the prosthetic socket and residual limb. These twisting forces are generated not only when turning while walking, but are present at some level even when walking in a straight line. This often causes soft tissue injuries from the socket and limb rubbing/twisting against each other. The absence of paired movement from the ankle and foot also causes the remaining muscles to compensate by working harder than they normally would during activities like walking.

Purpose:

The purpose of this study is to develop a new prosthesis, the **Pivot-Flex Foot (PFF),** that mimics the natural pairing motion of the intact limb and determine if this reduces the twisting force on the socket and compensatory effort, and increases satisfaction, when compared to a standard-of-care prosthesis.

Methodology:

This study will take place in two parts.

1) Participants with a unilateral transtibial (below-knee) amputation (up to 40) will be fit with our motor-driven and computer controlled **torsionally adaptive prosthesis (TAP)**. The TAP can pair turning and flexing motion at different proportional settings; several paired motion ratio settings of turning (transverse plane motion) to flexing (sagittal plane motion) will be tested. Over two visits, participants will do a series of walking tests over level ground with the TAP set at different pairing settings (blinded and random order) while biomechanical data is collected. Satisfaction data will be collected for each setting. The results will be used to inform the design of the PFF.

Based on results from the TAP testing, we will design and build PFFs of various sizes and stiffnesses to compare to a standard-of-care prosthesis. In a blinded crossover experiment, over 3 visits, participants (up to 40) will be fit with the study prostheses (PFF or a standard-of-care prosthetic foot) in random order and wear each study prosthesis at home for 2 weeks. Participants will visit the laboratory to do a series of walking tests after each 2-week acclimation period.

List of Abbreviations

AE – adverse event

CPRS - Computerized Patient Record System

CRQ – Continuing Review Questionnaire

HIPAA – Health Insurance Portability and Accountability Act

ISO - Information Security Officer

IRB – institutional review board

PFF – Pivot-Flex Foot

PHI – protected health information

PI – Principal Investigator

PO – Privacy Officer

ROP – report of other problem

SA – specific aim

SAE – serious adverse event

SD – standard deviation

TAP – torsionally adaptive prosthesis

TT – transtibial

UW – University of Washington

VA – Veterans Affairs

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1.0 Key Study Personnel

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2.0 Introduction

Amputees are prone to pain and injury caused by loads applied to the residual limb through the prosthetic socket [25-29]. Epidermoid cysts, for example, are painful lesions of the residual limb caused by shear stress where the skin of the residual limb rubs against the brim of the socket [18]. The high stress at the prosthesis-residual limb interface may also cause decreases in venous return and reduce lymphatic drainage, which can be detrimental to amputees with compromised vascular systems [18, 19, 28]. Transverse-plane moments, which peak during turning maneuvers, can exacerbate the problem [23, 30]. If turning maneuvers were uncommon, little emphasis on this problem would be warranted. However, turning maneuvers comprise a sizeable fraction of the steps taken during typical daily activities [31-33]. Amputees also experience back pain at a higher rate than the general population [34], resulting in part from an asymmetric gait [20]. Undesirable transverse-plane moments may be a factor in asymmetrical, compensatory gait.

The need to ameliorate transverse-plane moments between the residual limb and socket was recognized as early as 1947 by Eberhart [35] who wrote that transverse-plane motions and their frictional effects “are a major source of discomfort and the chief cause of dissolution of the skin.” Three decades later, Lamoureux and Radcliffe [36] presented a prosthesis with an elastomeric spring in between the ankle and the socket, and found that its use provided “dramatic relief of skin abrasions and epidermoid cysts in some cases”. In addition to reducing the transverse-plane moment, they also found improved gait symmetry. Today, transverse rotation adapters are commercially-available and can increase transverse-plane rotation and decrease transverse-plane moments [23, 37]. They may also improve the walking performance of bilateral amputees [38] and reduce the energy consumption of unilateral amputees at walking speeds above normal [39].

These observations suggest that prescription of transverse-plane torsion adapters may lead to greater mobility for lower limb amputees. However, their use is not widespread and if excessively compliant, may reduce gait stability [24]. Cost, weight, prosthesis build height, and the inability for the user to adjust the stiffness may all play a role in their lack of adoption, but it may also be that the transverse-plane rotation is not coupled with the sagittal-plane. With these devices, motion only occurs in the transverse-plane when a transverse-plane torque is applied. In contrast, the intact foot and ankle contain a complex set of joints that allows rotation in all three planes, and in particular, motion in the transverse- and sagittal-planes are coupled [15]. Such coupling in a lower limb prosthesis might be beneficial.

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 [40], the direct U.S. hospital costs related to these procedures could be conservatively estimated to exceed $350M annually [41]. Available data suggests the VA performs between 3000 and 5000 lower limb amputation surgeries on veterans of diabetic and dysvascular etiology each year [2, 42]. These veterans are among the 623,000 Americans who live with a major lower limb amputation [5], a population whose growth due to diabetes doubled between 1990 and 2008, but has since fortunately plateaued [43] 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 [4]; n=1645 major limb amputation (battle injuries) from 7Oct2001 to 1Jun2015 [44]). 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.

For veterans with lower limb amputation who are capable of locomotion, the VA clinician must choose among several hundred available prosthetic feet when prescribing a prosthesis. While these products have many different distinguishing features, none mimic the coupled motion exhibited by the natural limb. This project seeks to improve the ability of veteran lower limb amputees to ambulate by restoring coupled motion between the transverse- and sagittal-planes. The *clinical significance* of this research is the development of a passive, biomimetic limb that may help veterans achieve their rehabilitative goals.

3.0 Specific Aims and Hypotheses

(1) To identify the optimal coupling (pairing) ratio between transverse plane (*horizontal rotation*)- and sagittal plane (*flexing forward and backward*) motions using a novel, torsionally adaptive prosthesis (TAP). Our *general hypotheses* are:

> (H1) a coupling ratio exists between 0 (no coupling) to 1:2 (1° transverse-plane motion for every 2° sagittal-plane motion) that minimizes transverse-plane socket torque
>
> (H2) an amputee preferred coupling ratio will exist within this range. We will use the results of this experiment to specify the coupling ratio of the Pivot-Flex Foot used in specific aim 2.

(2) To determine if a passive prosthesis with an optimal coupling ratio (Pivot-Flex Foot) can reduce transverse-plane socket torque and compensatory gait biomechanics when compared to a standard-of-care prosthetic foot. Our *general hypotheses* for the different ambulatory activities are:

> (H3) the peak transverse-plane socket torque will be significantly different between the Pivot-Flex Foot and the standard-of-care prosthetic foot
>
> (H4) the positive sagittal-plane work done at the hip joint will be significantly different between the Pivot-Flex Foot and the standard-of-care prosthetic foot

4.0 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, 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.

5.0 Study Procedures

5.1 Study Design

This study will take place in two parts and will have two consent forms, one for each part of the study. Participants may be asked to be involved in both parts of the study. Participants will be men and women age 18-75 years old who have a unilateral transtibial (TT) amputation and have used a prosthesis for at least 6 months. Targeted enrollment for each part of the study is listed in the table below. Vulnerable populations will not be specifically targeted for enrollment. See inclusion/exclusion criteria below in section 5.4.

Participants with unilateral TT amputation – Study Total	80
Part 1 - Using the TAP, a motor-driven computer controlled prosthesis, to inform development of the PFF	40
Part 2 – Build and Evaluate the PFF	40

See section 5.5 below for data collection procedures and risk management.

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, all references to clinician approach letters refer to the *Clinician Approach Letter* attachment.

Recruitment Activities at the VA

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 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 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 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 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.

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.

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.

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 18-75 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) Prescribed prosthesis can accommodate fitment of the study prosthetic components to be tested (determined at initial visit)

Additional inclusion criteria for part 2:

6) Weigh 200lbs. or less
7) Wear a size 27-29 prosthetic foot

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

Additional Exclusion Criteria for part 2:

1) Peripheral neuropathy with impairment of protective sensation in the residual limb below a 5 of 10 point/site threshold (determined via Semmes-Weinstein monofilament testing at initial visit; i.e., participants must be able to feel at least 5 of 10 sites that are tested with the Semmes-Weinstein monofilament). Additionally, the participants' visual perception must be adequately intact to make a reasonable assessment of the skin condition of their residual limb (i.e., to see whether or not a wound is present). The research prosthetist will use clinical judgement to determine if the study is an appropriate fit.

5.5 Study Visits, Data Collection, and Risk Management

Visits and length of participation

This study will take place in two parts and will have two consent forms, one for each part of the study. Participants may be asked to be involved in both parts of the study; recruitment efforts will take place separately.

Part 1: Using the TAP, a motor-driven computer controlled prosthesis, to inform development of the PFF.

During this part of the study, we will use the TAP to evaluate several different paired turning and flexing motion ratio settings. Based on the results we will select an optimal paired ratio setting(s) that will be used in the design of the PFF.

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 two visits that may last up to 4 hours each. 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.

Visit 1

Eligibility

Participants' residual limb, prosthesis, and fitment will be examined to determine if they can participate in the study. The research prosthetist may adjust their prosthesis to optimize fitment. If a participant is unable to continue in the study they will be compensated for their effort.

Demographic Information

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

- Sex
- Race
- Ethnicity
- Veteran status

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

- Age
- Years since amputation
- Level and side of amputation
- Cause of amputation
- Body weight
- Height
- Prosthesis information (socket, liner, suspension, and foot type, category, and/or size

Self-Selected Walking Speed (SSWS) Tests

Participants will use their own prosthesis during these tests. Participants will be asked to walk several times, at their self-selected pace, for about 65-feet back and forth in a straight hallway. Participants will also be asked to walk at their own pace several times around a ~3-

foot radius circle. These tests will be used to determine each participants' straight line and circle SSWS.

Motion and Force Measurement

Participants will be asked to change into a tight-fitting shirt and shorts that we provide. A private area for participants to change clothes will be provided. We will record a series of standard body measurements such as height, weight, and leg length. We will attach up to 70 small reflective markers with double sided tape to specific locations on the participants' hands, trunk, legs, and feet.

During the walking tests in the lab, the infrared cameras will record the location and movement of the markers; they do not record a picture of the body. Data will also be collected by force plates embedded in the floor of the lab; participants will walk across and stand on the plates during the tests.

Torsionally Adaptive Prosthesis (TAP)

The research prosthetist will fit the TAP to the participants' socket. The TAP is a motorized, programmable prosthesis, it will be connected to a computer and power source with long wires. The wires will be routed so they are not a trip hazard. The TAP will be programmed with 5 different paired turning and flexing motion ratio settings. The different settings will change how the prosthesis feels (more or less compliant) during walking. Participants will practice walking on each of the settings until they feel confident/stable. If confidence and stability cannot be achieved the participant may not be able to continue in study.

The TAP's 5 paired motion settings will be tested in a randomized order. The first setting will be selected then participants will be asked to walk back and forth in a straight line several (approximately 3-6) times at their SSWS. Once we have enough data, participants will be asked to rate their satisfaction with the setting on a 0-10 scale. The same process will be repeated for each of the remaining settings.

After all five settings have been tested the research prosthetist will re-fit the participants' as-prescribed prosthesis. We will schedule the next study visit before participants leave or we will call them later to schedule it.

Visit 2

The procedures listed under "Motion and Force Measurement" will be used again during this visit. The research prosthetist will fit the TAP to participants' socket and they will be allowed to practice walking with it until they feel confident/stable.

The TAP's five settings will be tested in a randomized order. The first setting will be selected then participants will be asked to walk around a ~3-foot radius circle several (3-6) times at their SSWS. Participants will be asked to do the circle walking tests in both clockwise and counter-clockwise directions (randomized order). Once we have enough data, participants will be asked to rate their satisfaction with the setting on a 0-10 scale. The same process will be repeated for each of the remaining settings.

After all five settings have been tested the research prosthetist will re-fit the participants' as-prescribed prosthesis. We will schedule the next study visit before participants leave or we will call them later to schedule it.

Part 2: Build and evaluate the PFF

Informed by the results of Part 1, we will design, build and thoroughly bench test our PFF. We will build the PFF in a few sizes, and in left and right foot configurations to accommodate for participant variability. When ready, we will test the PFF with participants as described below.

Visits and length of participation

Consent and data collection procedures will be done at the VA Puget Sound in Seattle and participants will wear study assigned prostheses at home/in the community. Participants will be asked to do three visits that may last up to 4 hours each. 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.

Visit 1

Eligibility

Participants' residual limb, prosthesis, and fitment will be examined to determine if they can participate in the study. The research prosthetist may adjust their prosthesis to optimize fitment. If a participant is unable to continue in the study they will be compensated for their effort.

Demographic Information *If a participant completed Part 1 of the study then we will not collect this information again.*

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

- Sex
- Race
- Ethnicity
- Veteran status

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

- Age
- Years since amputation
- Level and side of amputation
- Cause of amputation
- Body weight
- Height
- Prosthesis information (socket, liner, suspension, and foot type, category, and/or size

Self-Selected Walking Speed (SSWS) Tests

Participants will use their own prosthesis during these tests. Participants will be asked to walk several times, at their self-selected pace, for about 65-feet back and forth in a straight hallway. Participants will also be asked to walk at their own pace several times around a ~3-foot radius circle. These tests will be used to determine each participants' straight line and circle SSWS.

Randomization to Study Prosthesis – At Home Acclimation

Participants will be randomized to wear the PFF or the standard-of-care prosthetic foot for the next 2 weeks at home/in the community during their normal daily activities. The research prosthetist will fit the PFF or standard-of-care foot to the participants as-prescribed socket and suspension system. Participants will be blinded to prosthetic foot type. The prosthetic feet will be covered with a sock and cosmesis and participants will be instructed not to remove the coverings from the foot. Participants will practice walking on the assigned foot until they feel confident/stable. If confidence and stability cannot be achieved the participant may not be able to continue in study. Participants will be instructed to contact us if they have any problems or concerns with the study prosthesis during the 2-week acclimation period. We will arrange to make prosthetic adjustments if needed. We will store the participants' prescribed prosthetic foot during the at-home acclimation periods.

Visit 2

After wearing the study prosthesis for approximately 2-weeks participants will return to the lab to do a series of walking tests.

Motion and Force Measurement

Participants will be asked to change into a tight-fitting shirt and shorts that we provide. A private changing area will be provided. We will record a series of standard body measurements such as height, weight, and leg length. We will attach up to 70 small reflective markers with double sided tape to specific locations on the participants' hands, trunk, legs, and feet.

During the walking tests in the lab, the infrared cameras will record the location and movement of the markers; they do not record a picture of the body. Data will also be collected by force plates embedded in the floor of the lab; participants will walk across and stand on the plates during the tests.

SSWS Walking Tests

While using the study prosthesis, participants will be asked to walk back and forth in a straight line several (approximately 3-6) times at their SSWS. Participants will also be asked to walk around a ~3-foot radius circle several (3-6) times at their SSWS. They will be asked to do the circle walking tests in both clockwise and counter-clockwise directions (randomized order).

Study Prosthesis – At Home Acclimation

The research prosthetist will fit participants with the other study prosthesis. Participants will remain blinded to the foot type. Participants will practice walking on the assigned foot until they feel confident/stable. If confidence and stability cannot be achieved the participant may not be able to continue in study. Participants will be instructed to contact us if they have any problems or concerns with the study prosthesis during the 2-week acclimation period. We will arrange to make prosthetic adjustments if needed.

Visit 3

After wearing the study prosthesis for approximately 2-weeks participants will again return to the lab to do a series of walking tests. The Motion and Force Measurement, and SSWS Walking Tests described in Visit 2 will be repeated. The research prosthetist will re-fit participants with their as-prescribed prosthetic foot.

Applicable to Parts 1 & 2

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., bluring 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, 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 $50/hour for the first hour of each visit and then $30/hour for each remaining hour of each visit to the VA Puget Sound (for both parts of the study). Participants involved in Part 2 of the study will be paid $100 for each 2-week at-home acclimation period. 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. Checks will be mailed by the fiscal department about 6-8 weeks after each study visit or can be picked up at the VA Puget Sound within the same time frame. Participants that are screened out after consent will be compensated on a prorated basis as well as for any applicable travel compensation.

Risks and Risk Management

Risks associated with use of study provided prostheses and walking procedures

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 in the lab or while wearing a study provided prosthesis during the at-home acclimation periods) and/or discomfort (e.g., mild to moderate muscle soreness 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). 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. The motion analysis laboratory floor is clear of obstacles, level, dry, and rigid. Thus, walking in the lab is akin to walking on a well-maintained indoor floor. Participants will be instructed to inform us if they feel pain or discomfort during the procedures and we will stop the activities to address any reported issues as needed. Care will be taken to properly fit the prostheses. Participants will only be asked to walk at speeds they are comfortable with. To minimize the risk of TAP or PFF prosthesis 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. The standard-of-care prosthetic foot is a commonly used, commercially available foot. Participants will be instructed to exhibit caution while acclimating to walking with a new or modified prosthesis. This is the same instruction 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 assigned feet for about an hour in the laboratory setting, we do not expect any problems to arise during the two-week at home portion of the study. The study feet will be fit to the participants' current socket which will also help minimize the risk of skin irritation. Participants will be asked to contact us in the event of any study-related pain or injuries to schedule an examination.

In part 2 of the study, we may discover that participants have peripheral neuropathy with impaired sensation in their residual limb, or that the level of neuropathy or impaired sensation is different than participants were aware of. This may cause some level of stress. For dysvascular individuals, it is not uncommon for the residual lower-limb to have some level of

peripheral neuropathy with impairment of sensation. Semmes-Weinstein monofilament testing is a simple and non-invasive test normally administered to dysvascular patients to assess protective sensation on the level of the skin of the lower extremities. The selected monofilament test score threshhold should minimize the risk of dysvascular participants being unable to notice skin irritation on their residual limb. If participants become distressed during the Semmes-Weinstein monofilament testing we will advise them to see their regular care provider.

The tape used to apply the markers may cause mild skin discomfort or irritation while worn or when removed (feels similar to removing a band-aid). Only trained study staff will place and remove the reflective markers.Participants may feel embarrassed while wearing the tight fitting clothing.

It is also possible that participants may experience stress or inconvience by coming to the VA for multiple visits. Participants can stop their participation 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 study will 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.

5.6 Data Analysis

Specific Aim 1: Kinematic and kinetic data from the experiment will be analyzed to identify the peak transverse-plane moment of the straight and both directions of the circle walking trials at the five different coupling ratios (0, 1:6, 1:4, 1:3, and 1:2). This data will be processed (Visual3D; C-Motion, Germantown, MD) and aggregated using project specific software (Matlab; Mathworks, Natick, MA).

We hypothesize that:

H1.1: When walking in a straight line, there exists a coupling ratio that minimizes the peak transverse-plane moment.

H1.2: When circle walking with the prosthetic limb on the inside of the turn, there exists a coupling ratio that minimizes the peak transverse-plane moment.

H1.3: When circle walking with the prosthetic limb on the outside of the turn, there exists a coupling ratio that minimizes the peak transverse-plane moment.

The statistical analysis to test these hypotheses (H1.1, H1.2, and H1.3) will require three linear mixed effects regression analyses. These analyses will test for differences between the five coupling ratios across the three different ambulatory activities with random effects for subject and subject by coupling ratio 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 lme4 and multcomp packages, Vienna, Austria). Exact p-values will be reported for each test.

We conducted an exploratory power analysis for hypothesis **H1.1**: The peak torque at the interface between the socket and the residual limb will be significantly different between a passive prosthesis that couples transverse-plane rotation with ankle dorsiflexion and the standardized study prosthesis. For this within-subject randomized crossover study design, we used recently analyzed data (n=1) to compare the effect of a coupling ratio of 0 with 1:2. The difference in peak socket torque was 19% between the two coupling ratios with a standard deviation of 17% between peaks. We calculated 98 percent power to find a significant difference between the test prostheses at $p<0.05$ for 15 subjects.

Satisfaction data from the experiment will be tabulated for straight and both directions of the circle walking trials at the five different coupling ratios (0, 1:6, 1:4, 1:3, and 1:2). This data will be processed and aggregated using project specific software (Matlab; Mathworks, Natick, MA).

We hypothesize that:

H2.1: When walking in a straight line, there exists a coupling ratio that maximizes satisfaction.

H2.2: When circle walking with the prosthetic limb on the inside of the turn, there exists a coupling ratio that maximizes satisfaction.

H2.3: When circle walking with the prosthetic limb on the outside of the turn, there exists a coupling ratio that maximizes satisfaction.

The statistical analysis to test these hypotheses (H2.1, H2.2, and H2.3) will require three Friedman analyses of variance (ANOVA). These analyses will test for differences between the five coupling ratios across the three different ambulatory activities. 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 VA enterprise software (SPSS Statistics v22; IBM, Inc.). Exact p-values will be reported for each test.

The results of testing hypothesis 1 will be used to define the optimal coupling ratio. The coupling ratios (0, 1:6, 1:4, 1:3, and 1:2) will be placed in rank order and an evenly weighted rank average will be used to identify the coupling ratio that minimizes the transverse-plane moment. If this algorithm cannot distinguish between two or more coupling ratios, then a similar method will be used to rank the results from hypothesis 2. If neither algorithm can distinguish the optimal coupling ratio, then the investigative team will engage the clinical

team and use their experience to select a coupling ratio for use in specific aim 2. Please see our discussion of this issue in the potential problems section.

Specific Aim 2: Kinematic and kinetic data from the experiment will be analyzed to identify the peak transverse-plane moment and hip work while walking straight and in both directions of the circle walking trials while wearing the study prostheses. This data will be processed (Visual3D; C-Motion, Germantown, MD) and aggregated using project specific software (Matlab; Mathworks, Natick, MA).

We hypothesize that:

H3.1: When walking in a straight line, the peak transverse-plane moment will be significantly different between the Pivot-Flex Foot and the standard-of-care prosthesis.

H3.2: When circle walking with the prosthetic limb on the inside of the turn, the peak transverse-plane moment will be significantly different between the Pivot-Flex Foot and the standard-of-care prosthesis.

H3.3: When circle walking with the prosthetic limb on the outside of the turn, the peak transverse-plane moment will be significantly different between the Pivot-Flex Foot and the standard-of-care prosthesis.

H4.1: When walking in a straight line, the positive sagittal-plane work done at the hip joint will be significantly different between the Pivot-Flex Foot and the standard-of-care prosthesis.

H4.2: When circle walking (steady-state turning) with the prosthetic limb on the inside of the turn, the positive sagittal-plane work done at the hip joint will be significantly different between the Pivot-Flex Foot and the standard-of-care prosthesis.

H4.3: When circle walking (steady-state turning) with the prosthetic limb on the outside of the turn, the positive sagittal-plane work done at the hip joint will be significantly different between the Pivot-Flex Foot and the standard-of-care prosthesis.

Our interest in the positive sagittal-plane work done at the hip joint stems from the lack of propulsive power produced by passive prosthetic feet during ambulation by individuals with lower limb amputation. While energy storing and returning prosthetic feet can provide some propulsive assistance, the positive sagittal-plane ankle joint power and work produced is far below that provided by the ankle-foot musculature of the intact limb (e.g., [56, 57]). Individuals with lower limb amputation compensate with greater sagittal-plane hip joint power and work, which is likely one of the reasons why they walk slower and at higher metabolic cost than their intact counterparts (e.g., [17, 58-60]). Our preliminary results with the TAP suggest that when the coupling ratio was increased: (1) prosthetic-side positive hip work may decrease during straight walking and prosthesis-on-the-outside during circle walking, and (2) prosthetic-side negative hip work may decrease during prosthesis-on-the-outside during circle walking. Both are desirable outcomes as they may reduce the biomechanical effort associated with walking.

The statistical analysis to test these hypotheses (H3.1, H3.2, H3.3, H4.1, H4.2, H4.3) will require six linear mixed effects regression analyses. These analyses will test for differences by

foot type (Pivot-Flex Foot or standard-of-care) with random effects for subject and subject by foot type 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.

An exploratory power analysis for peak transverse-plane moments was performed using mean values from Orendurff et al. [61] exerted by able bodied subjects performing a turning task. In Orendurff's study, subjects (n=10) completed a 270° turn around a one meter circle with a peak ankle rotational torque of 0.167 ± 0.011 Nm/kg for the inside limb. Assuming a 10% within-subject difference between study prostheses and that the standard deviations are like those of Orendurff's, there is over a 97% chance to find a significant difference between stiffness settings for 15 participants.

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 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.

6.0 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 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.

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, 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 (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 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.

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.

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