Development of Adaptive Vacuum Suspension to Improve Prosthetic Fit and Residual Limb Health

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PROTOCOL + STATITICAL ANALYSIS PLAN

THE OHIO STATE UNIVERSITY

Contents

I .Background:

Achieving a comfortable and functional connection between an amputee and their prosthetic limb is critical to the success of the prosthesis. Therefore, the socket system is the most significant component for overall success of the prosthesis[1,2]. In an effort to maximize socket performance and comfort without adversely affecting residual limb health, a prosthetist custom fits a socket for every patient using plaster wraps or computer aided design. Currently, this process suffers from a lack of quantitative feedback to determine appropriate socket fit. Prosthetists aim to minimize suspension-dependent movement between the socket and residual limb, but current approaches are limited as they rely on anecdotal visual cues along with subjective verbal feedback from the patient. Prosthetists then use this information to revise socket parameters such as volume, geometry, and type of suspension to provide current 'best' fit for a patient. Regardless of prosthetist fitting, the volume of mature residual limb (>18 months post-amputation[3]) are subject to daily[4] and chronic[5,6] changes in volume that compromise socket fit and performance. For the 1 million Americans that live with a lower-limb amputation, a growing number of which are service men and women[7-9], these volume changes adversely affect fit, performance, and residual limb health[6] – including skin breakdown and ulceration[10] that can necessitate revision of the amputation. Indeed, for traumatic lower-limb amputations, the requirement for surgical revision is known to be as high as 30%[11].

II. Objective:

Aim 1 will evaluate the relationship between vacuum pressure and limb movement inside the socket and how it changes with respect to vacuum pressure setting, gait speed and socket volume

Aim 2 will evaluate the impact of socket movement on residual limb circulation and residual limb skin health

Aim 3 will compare the effectiveness of an adaptive vacuum system to standard of care suspension prosthetics (pin-locking or suction).

Study Population: Up to 170 amputees will be enrolled in the study overall.

1. **Aim 1:** 10 trans-femoral amputees and 10 trans-tibial amputees will be enrolled.
2. **Aim 2:** 15 trans-tibial and 15 trans-femoral amputees will be enrolled.
3. **Aim 3:** n=120 (trans-tibial and trans-femoral amputees) will be enrolled.

III. Inclusion Criteria:

1. Ages of 18 and above

2. Unilateral trans-tibial or trans-femoral amputee
3. Ambulate at a K2 level or higher
4. At least 3 months post-amputation per physician discretion
5. Residual limb length greater than 6.5 inches in length
6. Able to follow directions and give informed consent on their own or through Legally Authorized Representative.
7. Must be able to ambulate without assistance. An external assistance device such as cane or walker will be permitted**.**

8. Adequate arterial blood flow of the index stump as evidenced by TcOM > 30 mmHG, measured within the past 12 months.

IV. Exclusion Criteria:

1. Conditions that prevent wearing a prosthetic socket; such as existing scab, ulcer, or keloid scar on amputation stump.
2. Cognitive deficits or mental health problems that would limit ability to consent and participate fully in the study protocol
3. Women who are pregnant or who plan to become pregnant in the near future

V. Study Design: This study has 3 aims where trans-femoral and trans-tibial amputees will be enrolled.

Subjects enrolled in Aim 1 (N=20) will have one study visit that will take place at The Ohio Willow Wood (OWW).

Subjects enrolled in Aim 2 (N=30) will have a total of 4 visits at baseline, month 1, month 2, and month 3.

Subjects in Aim 3 (120) will be enrolled at Indiana University (n=30 subjects), OWW (n=30), and at Walter Reed National Military Medical Center (WRNMMC) (n=60 subjects) with a total of 3 visits at 0 week (baseline), 0-4 weeks (socket fitting visits), and 16 weeks (final visit).. OWW and Walter Reed National Military Medical Center (WRNMMC) have separate IRB protocol & approval to conduct their part of subject recruitment and study visits. Aims 2 and 3 will not be run concurrently. Subjects enrolled in Aim 2 can participate in Aim 3. Aim 2 studies performed at Ohio State and Indiana University. Aim 2 has enrolled 15 subjects through Ohio State University & OWW (and these 20 subjects have completed their participation in the study) and the data is currently being analyzed to determine if additional subjects are required. If analysis shows sufficient subjects have been enrolled to achieve the study aim, no additional subjects will be enrolled in Aim 2. If there is insufficient data, the remainder of the Aim 2 subjects will be enrolled through OWW under their approved IRB with WIRB. Aim 3 studies performed at IU, OWW and WRNMMC per their approved IRB protocols. The vacuum suspension used for the study is new to all enrolled subjects

We are requesting the use of ResearchMatch.org for subject recruitment on this protocol. See attached General Description of ResearchMatch attached.

Descriptions of prosthesis suspension platforms:

Pin-locking prosthesis: A gel-liner with an attached pin, lanyard, KISS system that clicks into a locking mechanism (receiver) inside the socket.

Suction prosthesis: A total contact weight bearing socket with a one-way expulsion valve to let air out.

Adaptive vacuum test prosthesis ("test" system): The adaptive vacuum prosthesis is sold as a commercial device by the company Willow Wood with suggested U.S. L-Code L5781. The device is designated as a Class 1 Medical Device and 510(K) Exempt. This category is part of a low or moderate risk to patient safety and health. The Prosthetic socket system uses an active vacuum pump to push air out of the socket. The level of vacuum is controlled by hardware that automatically detects the socket fit based on in-socket motion and adjusts vacuum as needed to eliminate this motion.

VI. Aim 1 (Completed):

1. **Study Visit 1** This initial visit will take place at The Ohio Willow Wood and the following research activities will take place:
    - Informed Consent will be obtained
    - Baseline demographics, medical history, and medications will be recorded
    - Verify fit of the thermoplastic socket
    - Subject will perform multiple ambulation trials at controlled cadences while the vacuum pump is set turned off (0 inHg), 7 inHg, 10 inHg, 13 inHg, and 20 inHg.
    - Subject will repeat the ambulation task with different thickness liners to simulate global volume changes.
    - Subject will repeat the ambulation task with a gel pad insert to simulate local volume changes.

VII. Aim 2 (partially completed if additional subjects are needed, they will be recruited at OWW with their approved IRB protocol):

1. **Study Visit 1 (Baseline)** This initial visit will take place at OSUWMC & OWW where the following research activities will take place:
    - Informed Consent will be obtained

- Baseline demographics, medical history, and medications will be recorded
- Subjects will perform seated tasks, standing tasks, and walking on a treadmill task. Skin health measurements will be taken before and after the activity period.
- Hyperspectral Imaging – A non-invasive visible light imaging technology will measure tissue oxygenation
- Hitachi Aloka Ultrasound – A hand held device will be moved gently across the skin and measure your blood flow of deeper skin tissues.
- Skin Temperature-A small tab (small sticker) will be placed on the skin and tell us the temperature of your residual limb
- Surface Electrical Capacitance – Small non-invasive probe place on skin to measure skin hydration
- Trans epidermal water loss measurement (TEWL) – Small non-invasive probe compares relative humidity of skin surface to indicate epidermal barrier function
- Transcutaneous Oxygen Measurement – Small non-invasive probe measures the amount of oxygen released through the skin layer
- This data will be used to determine how socket movement affects the limb health measurements
- The study prosthetist will set vacuum level set to first level
- Digital Image

2. **Study Visit 2, 3, 4 (month 1, 2, 3)** Subjects will return at 1, 2, and 3 months after study visit 1 where the following research activities will take place:
    - Subject will perform seated tasks, standing tasks, and walking on a treadmill task. Skin health measurements will be taken before and after the activity period.
    - Hyperspectral Imaging
    - Hitachi Aloka Ultrasound
    - Skin Temperature
    - Surface Electrical Capacitance
    - TEWL measurement
    - Transcutaneous Oxygen Measurement
    - This data will be used to determine how socket movement affects the limb health measurements
    - The study prosthetist will set the vacuum level set to the next treatment level except at study visit 4.
    - At the end of visit 4, patients will be returned to their standard of care prosthesis. The study prosthetist will be available to review and adjust the fit of their existing prosthesis.
    - Digital Image

VIII. Aim 3 (n=30 will be performed at IU under current approved protocol):

Rationale for the amendment: As per the approved DoD proposal, n=60 (n=30 each at IU and Willow wood for Limb Heath analysis, current approved IU IRB protocol) and n=60 subjects were supposed to be completed at Walter Reed (WR) for Functional analysis. We have received a request from WR to perform Functional analysis on the remaining subject that will be enrolled for limb health analysis (this is due to COVID-19 and availability of subjects at WR. The request from WR was also in view of short time line remaining (study end date 09/2021).

After receiving consent, the first enrollment visit will be scheduled for the subjects to see the IU study prosthetist to initiate the "test" socket fitting visits.

On this day, prior to socket fitting activities, the arterial blood flow will be measured on the index stump if not already completed per standard of care within the previous 12 months prior to enrollment for data analysis. Those with an TcOM < 30 mmHG be excluded and no further study activities will be completed. These subjects will be recorded as a screen fail and will not be enrolled.

Others will move forward with socket fitting activities.

A. Study Visit #1 - Socket Fitting visits (Week 0 - 4, +/- 2 weeks) – ***Note: this visit may consist of three (minimum) visits plus socket adjustment visits (as needed by the subject) on separate days (up to 4 weeks)***

- **i) limb shape capture, measurements or tracing**
- **ii) diagnostic static fitting and diagnostic dynamic fitting**
- **iii) delivery of definitive "research" socket**

Once delivery of the definitive research socket has been completed, the subject will be allowed to return for no greater than 4 adjustments (within 0-2 weeks from baseline) to obtain a comfortable fit in order to complete this study. If subject requires more than 4 adjustment visits, the participation from the study will end.

Once the subject is comfortable with the fitting, the date will be noted by the study team as "**research socket use start date"**. From this date, the subject will begin wearing the test socket for next 16 weeks.

B. Study Visit #2A - Baseline visit for residual limb health (Week 4, +/- 2 weeks) Enrollment, after delivery of the definitive research socket and completion of the socket fitting visits, the following research activities will take place to obtain baseline measurements:

- Subjects will be asked to walk on a treadmill for 10 mins. The residual and sound (intact) limb health measurements will be taken before and after the activity period with the exception of conducting post-activity ultrasound and digital imaging. The purpose of acquiring ultrasound and digital imaging is to determine changes in skin structure on a long-term basis; thus, these measurements will only be collected during pre-activity procedures to observe changes in a resting state. The following health measurements will take place:
    - Surface Electrical Capacitance
    - TEWL measurement
    - Hyperspectral Imaging
    - Ultrasound (pre-activity only)
    - Perfusion/ Blood flow
    - Digital Image (pre-activity only)

B.i. Study Visit #2B - Baseline visit for gait assessment (Week 4, +/- 2 weeks)**

***Note* Study Visit #2A and #2B can be combined and performed in a single study visit upon the discretion of the subject.**

Subjects will begin in their current standard of care prosthesis (the prosthesis worn at time of study enrollment), wherein the following research activities will take place in the following order:

- Subjective questionnaires [Veterans RAND 36-Item Health Survey (VR
- 36, PEQ, Socket Comfort Scores (SCS), and National Institute of Health (NIH) Patient-Reported
- Outcomes Measurement Information System (PROMIS)
- Functional evaluation [Comprehensive High-level Activity Mobility Predictor (CHAMP)]
- Biomechanical evaluation of gait during 6min walking test
    a. Positioning markers will be placed on the subject while performing the walking assessment to track and describe the movement of the body in three dimensions.
- Repeat SCS outcome

**** applicable to any new enrollments and/or any already enrolled subject completed their limb health part (16 weeks in test sockets followed by 4 weeks in SoC socket as wash off period)**

Following completion of these activities in study visit 2A & B, the subjects will be fitted with the adaptive vacuum suspension by a certified prosthetist that they will wear subsequently wear the device for 16 weeks

The study team will follow up subjects with a weekly phone call to determine the compliance for the use of research socket.

C. **Study Visit #3A – Final Visit (Week 16, +/-2 weeks).** After 16 weeks of wearing the "research" socket the following research activities will take place in the following order:

- Subjects will be asked to walk on a treadmill for 10 mins. The following residual and sound limb health measurements will be taken before and after the activity period with the exception of conducting post-activity ultrasound and digital imaging, is as follows
    - Surface Electrical Capacitance
    - TEWL measurement
    - Hyperspectral Imaging
    - Ultrasound (pre-activity only)
    - Perfusion/ Blood flow
    - Digital Image (pre-activity only)

C.i **Study Visit #3B–** the visit will take place either the same day of Visit 3A or another day within the Week 16, +/-2 weeks based on subject convenience, to repeat research activities previously performed in study visit # 2A

- Subjective questionnaires [Veterans RAND 36-Item Health Survey (VR 36, PEQ, Socket Comfort Scores (SCS), and National Institute of Health (NIH) Patient-Reported Outcomes Measurement Information System (PROMIS)
- Functional evaluation [Comprehensive High-level Activity Mobility Predictor (CHAMP)]
- Biomechanical evaluation of gait during 6min walking test
- Repeat SCS outcome

- The subjects will be given a choice to keep the research socket or return to using their original prosthesis as normal. The study prosthetist will be available to review and adjust the fit of their standard of care prosthesis at this time. Note; Due to physical change and limb volume fluctuation over the study period, it is possible that at the end of the study the standard of care prosthesis will not fit your residual limb as it does at the beginning of the study. At the completion of the study it is recommended that the subject follow up with their primary care prosthetist for socket evaluation and fitting.
- Any research-related tests or activities are performed at the expense of the research study and will not be billed to you or your insurance.
- Any non-research related activities, tests, or necessary medical treatment will be provided to you and billed as part of your medical expenses. Costs not covered by your health care insurer will be your responsibility. Also, it is your responsibility to determine the extent of your health care coverage.

Walter Reed National Military Medical Center (WRNMMC) will recruit and enroll 60 subjects with a pin-locking prosthesis and has separate IRB approval to conduct the study. The study visits will be per their approved IRB protocol (see attached).

IX. Study Procedures:

There may be risks that are not known about at this time. Side effects, risks, and discomforts may result from study participation.

A. Demographic, medical, and subjective questionnaires: Subjects will be queried on self-reported measures of user comfort and performance. Briefly, four subjective measures will be completed: VR-36, PEQ, SCS, and measures from the NIH PROMIS. The VR-36 was developed from the original RAND version of the Medical Outcomes Study 36-Item Health Survey as a short form functional assessment for veterans. The PEQ is composed of 9 validated scales to measure various aspects of a prosthesis and the users feelings about it. The scales include: Ambulation, Appearance, Frustration, Perceived Response, Residual Limb Health, Social Burden, Sounds, Utility, and Well Being. The SCS is based on a 0-10 numerical scale that assesses comfort rather than pain. The SCS will be administered by asking the participant: "If 0 represents the most uncomfortable socket fit you can imagine and 10 represents the most comfortable socket fit, how would you score the comfort of the socket fit of your artificial limb at the moment?". The NIH developed a system of reliable, precise measures to be used to capture patient-reported physical, mental, and social well-being. The PROMIS tools are aimed at helping clinical researchers most appropriately quantify how a patient is feeling or what they are able to do.

B. Comprehensive High-level Activity Mobility Predictor (CHAMP) Test: The CHAMP test will be used to assess overall amputee performance and the effect of the socket suspension intervention over time. The conglomeration of clinical assessment tools into the CHAMP was specifically done to measure high-level mobility in service members with a lower limb amputation. CHAMP consists of the Single Leg Stance Test (SLS), the Edgren Side Step Test (ESST), Illinois Agility Test (IAT), and T Test. The SLS measures the time an amputee is able to stand in single support with their hands on their hips and is performed with eyes open and with eyes closed. The ESST measures the ability of the participant to side shuffle back and forth in the layout shown in Figure 20 for 10 seconds. A point is given for each cone passed which is totaled for the 10 seconds. The IAT and T-test requires additional agility and control to navigate the course. Participants will complete the tasks in the following order: SLS, ESST, T-Test, and IAT. To generate a composite CHAMP score, the best times or point for each task is converted to a 0-10 scale following the scoring system. The

composite CHAMP score will range from 0-40, with 40 representing the highest level of performance.

C. Biomechanical evaluation of gait: IU Neuroscience Gait lab will be used to collect kinematic data. The laboratory is equipped with an instrumented treadmill and infrared camera system. A harness system will be used to provide support and safety for the amputees while study participants walk on the treadmill for 6 minutes. A specially designed reflective marker set, will track movement between the socket and residual limb and allow analysis of motion not detected by the vacuum system, to quantify and characterize soft-tissue specific pistoning across suspension platforms. Reflective passive markers will be placed on the amputee and prosthesis, including the socket. A virtual marker position will be created for the residual limb from the physical markers. A series of segment definitions will be based off the reflective marker positions. The 3-dimensional position and orientation of a segment will be tracked relative to the segment immediately proximal using transformation matrices.

D. Transcutaneous Oxygen Measurement and skin temperature:
The PeriFlux System 5000 uses non-invasive probes that will measure the skin temperature and transcutaneous Oxygen Measurement. The probe head is affixed to the residual limb by an adhesive sticker.

E. Hyperspectral Imaging for tissue oxygenation and perfusion:
Powered by spatial frequency domain imaging, this imaging system provides a more complete picture of tissue health by quantifying and mapping tissue oxygenation and perfusion. Data are displayed in the form of color-coded maps.

X. Potential Risks:

There may be risks that are not known about at this time. Side effects, risks, and discomforts may result from study participation.

Prosthesis placement: While the goal of this project is to create a more comfortable prosthesis, it is possible that the subject could experience discomforts commonly associated with prosthesis use, such as perspiration, dry skin, rash, itching, blisters, high pressure in the socket, looseness in the socket, and mechanical rubbing that leads to ulceration which may lead to infection and additional surgery. Subjects with low levels of arterial blood flow have an additional risk of ulceration.

Treadmill task:

There is a risk of falling during the research activities. This risk is mitigated by the ability of participants to self-select pace for the treadmill task and observation of treadmill activities by research staff.

Transcutaneous Oxygen Measurement and skin temperature:
The PeriFlux System 5000 poses minimal risk to the subject. Removal of the sticker after data acquisition may cause minor discomfort similar to removing a small band-aid.

Hyperspectral Imaging for tissue oxygenation and perfusion:
This non-invasive non-contact imaging technique poses minimal risk to the subject.

Ultrasound:
Ultrasound imaging is a noninvasive technique and is a minimal risk procedure.

TEWL and Surface Electrical Capacitance Measurements:
TEWL and Surface Electrical Capacitance measurements are noninvasive and propose less than minimal risk.

Loss of Confidentiality
Although efforts are made to protect your study records, there is always a risk that someone could get access to your private health records.

XI. Unanticipated Problems and Adverse Event Reporting

Protocol deviations and Unanticipated Problems Involving Risks to Subjects or Others, Adverse Events, and Other Problems will be reported to the Indiana University per IU IRB reporting requirements.

Unanticipated problems can occur in any type of research (medical or non-medical) and may include occurrences such as adverse events, subject complaints, protocol deviations, and other untoward events involving risk. Events requiring prompt reporting by investigators and research staff may involve physical, psychological, social, legal, or economic harms.

Event reports and accompanying information will be screened for completeness by research staff members, additional clarifications will be requested from the investigator as necessary. Research staff members and the principal investigator will make an initial determination about whether the event represents a possible unanticipated problem involving risks to subjects or others and/or potential noncompliance. Reports of events determined during screening to represent possible unanticipated problems involving risks to subjects or others and/or serious/continuing noncompliance will be forwarded to the IRB for convened review. Reports of events that do not meet the requirements for prompt reporting may be reported at time of study renewal.

XII. Discontinuation Criteria

Patients will be informed during the informed consent process (in writing and verbally) that they are free to withdraw from the trial at any time. The Investigator may exercise his medical judgment to terminate a patient's participation in the trial due to clinically relevant changes in any clinical or laboratory parameter. The Sponsor-Investigator also reserves the right to discontinue/terminate the trial at any time.

Discontinuation criteria for individual subjects include: (1) Non-compliance with the inclusion/exclusion criteria, (2) treatment non-compliance, such as use of another socket, (3) withdrawal from the study due to reasons not related to the treatment.

XIII. Procedures for Amendment of Protocol:

Protocol modifications will be approved by the IU IRB prior to implementation and WRNMMC site HQ will be notified if the change is significant or adversely impacts the risk/benefit assessment for the study.

As per IU HRPP guidance on NSR devices reviews trial monitoring, an internal review of data/source verification will be performed and documented on a quarterly basis. The internal reviewer will will conduct the following activities: quarterly observation of research recruitment, informed consent process, research activities completed at research study visits, data collection and analysis. The internal review process may meet more frequently as deemed necessary and will be immediately notified of any serious and/or unanticipated event(s) related to procedures of the study. They will review all summary data, overall progress of the study and any individual serious and/or unanticipated event report(s). They do not have any conflicts of interest with the study team and/or protocol. In addition, a Data Safety Monitoring Board (DSMB) will provide independent oversight of the study, and will meet with the PI and research team at the following intervals: (1) prior to enrollment, after enrollment of the first 15 subjects for Aim 2, after enrollment of the first 30 subjects for Aim 3, and after all subjects have been enrolled and within 60 days of completion of the study for both Aims 2 and 3. The, DSMB will consist of a physician chairperson, a statistician, and a clinical trialist/ethicist. The Data Safely Monitoring Board will meet at the same intervals separate of the internal research reviewer. .

XIV. Payment:

All subjects will be compensated $100 for each of the completed visits. Aim 1 subjects will be compensated $100 for the completed study visit 1. Aim 2 subjects will have 4 total visits and will be eligible for a maximum of $400 for completion of all study visits. Aim 3 subjects will have 3 total visits and will be eligible for a maximum of $450 for the completion of all visits per following schedule: Visit #1 ($50), Visit #2A &B ($150, for completing all socket fitting activities

& baseline) and Visit #3A&B ($250). Subjects will not be paid if any of study visits are not completed.

XV. Statistical Analysis:

Patient demographics and clinical characteristics will be described using frequencies and percentages for categorical data and median and the interquartile range (IQR) for continuous data. In Aim 1, random-effects linear regression will be used to assess the relationship between wave amplitude and distal movement (or lateral shift) controlling for vacuum pressure. Patient ID will be the random-term in the model. In Aim 2, random-effects linear regression will also be used to compare percent change in limb perfusion across adaptive EVS and suction at 12 weeks controlling vacuum pressure and controlling for the baseline EVS and suction values. In Aim 3, a random-effects linear regression model will be used to establish the relationship in amputee performance (as measured by the CHAMP tasks) and residual limb health across EVS and suction and across EVS and pin-locking/lanyard in a cross-over design. The model includes terms for group (EVS vs. suction or EVS vs. pin-locking/lanyard), sequence (EVS to suction vs. suction to EVS or EVS to pin-locking/lanyard vs. pin-locking/lanyard to EVS), and visit (second vs. first). All statistical models will account for the effect of age, diabetes status and smoking history by including them as the covariates in the models. As per need, subjects may be stratified based upon diabetes status and arterial blood flow status. The *p*-values produced in the study will be adjusted using the Holms procedure to control the overall type I error at 0.05 due to the multiple comparisons. All analyses will be run using Stata 13.1, Stata Corporation, College Station, Texas.

XVI. References:

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