

Functional Performance Evaluation of NU-FlexSIV Socket

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PROTOCOL TITLE: Functional Performance Evaluation of the Northwestern University Flexible Sub-Ischial Vacuum (NU-FlexSIV) Socket for Persons with Transfemoral Amputation

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PRINCIPAL INVESTIGATOR:

Stefania Fatone, PhD, BPO(Hons)
Department of Physical Medicine and Rehabilitation
312-503-5717
s-fatone@northwestern.edu

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1.0 Objectives

1.1 Specific aims:

This proposal aims to provide evidence to support use of the NU-FlexSIV Socket for persons with transfemoral (above-the-knee) amputation. This will be accomplished by undertaking a prospective, assessor-blinded randomized cross-over trial comparing comfort and functional performance with the NU-FlexSIV Socket to the standard-of-care ischial containment socket in persons with unilateral transfemoral amputation.

The primary aims of the study are:

Aim 1: To demonstrate if the NU-FlexSIV Socket is more comfortable than the IC socket.

Aim 2: To demonstrate if the NU-FlexSIV Socket results in better functional performance than the IC socket.

Aim 3: To demonstrate the NU-FlexSIV Socket will result in better quality of life and “satisfaction with device” (i.e. prosthesis) than the IC socket.

1.2 Hypotheses to be tested:

Hypothesis 1: We hypothesize that the NU-FlexSIV Socket will provide increased comfort compared to the ischial containment socket.

Hypothesis 2a: We hypothesize that the NU-FlexSIV Socket will allow greater prosthetic side hip range of motion, in particular increased hip extension, leading to increased prosthetic side step length and hence walking speed compared to the ischial containment socket.

Hypothesis 2b: We hypothesize that step width and lateral trunk flexion over the prosthetic limb will not differ between the NU-FlexSIV Socket and ischial containment socket.

Hypothesis 2c: We hypothesize that the NU-FlexSIV Socket will result in faster times to perform the 5-Times Rapid Sit-to-Stand Test, Four Square Step Test and T-Test of Agility compared to the ischial containment socket.

Hypothesis 3: We hypothesize that the NU-FlexSIV Socket will result in better health-related quality of life and satisfaction with device as assessed using the OPUS compared to the ischial containment socket.

2.0 Background

2.1 Relevant prior experience and gaps in current knowledge:

Current prosthetic sockets restrict function, lack comfort and cause secondary health problems. Although designed to support the body and enable effective biomechanical load transfer during walking and other activities, prosthetic sockets interface with residual limb tissues that are neither accustomed nor well-suited to

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the high pressure and shear loading that occurs during ambulation with a prosthesis. Despite high daily use (>12 hours), lack of socket comfort is the most common complaint of prosthesis users. Prosthetic sockets lead to many issues due to high pressure, shear stress, temperature and moisture, all of which are exacerbated in highly active persons with amputation and those with irregular residual limbs (e.g. due to traumatic amputation that have irregular shape, extensive scarring, invaginations, skin grafts, painful neuromas, etc.). Residual limb skin problems include cysts, calluses, verrucous hyperplasia, allergic reactions, and bacterial or fungal infections. Residual limb skin problems have been reported by 25% to 63% of persons with amputation in the general population and problems have a negative influence on ability to perform household tasks, prosthesis use, social functioning, and participation in sports.

Sub-ischial sockets challenge conventional understanding of the biomechanics of transfemoral sockets, especially regarding coronal plane stability. In able-bodied walking, the hip abductors, primarily the gluteus medius, maintain pelvic control during single limb stance. Contraction of the hip abductors counters the moment created about the hip by the body center of mass and helps to keep the pelvis level and trunk upright. When the abductors are compromised, lateral trunk lean over the stance limb may be observed (often referred to as a Trendelenberg gait). In the IC socket, skeletal contact over the medial aspect of the ischium and greater trochanter, create a medial-lateral ‘skeletal lock’ for coronal plane control. For sub-ischial sockets, these forces still remain but the socket geometry believed necessary to control them is gone.

The mechanism by which transfemoral prosthetic sockets provide coronal plane stability during gait has been recently debated. Dillon (2007) stated that in an IC socket coronal plane pelvic stability is derived almost entirely from containment of the ischium and ischial ramus and that when containment is not achieved, coronal plane stability is poor. Dillon (2007) has also argued that the ability of any socket to provide coronal plane stability relies in part on the soft tissue, especially the adductors, being compressed to increase stiffness. Compression of soft tissues may occur to a larger extent when vacuum-assisted suspension is used because both the liner and socket are considerably under-sized, potentially contributing to coronal plane stability.

In contrast to existing transfemoral sockets, the NU-FlexSIV Socket does not impinge on the pelvis because it has lower proximal trim lines; is highly flexible allowing muscles to move comfortably within the socket as they contract during activity and improving sitting comfort; and is held securely to the residual limb by suction from a vacuum pump as well as compression from the liner and socket being undersized, making for a firmer connection to the prosthesis.

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2.2 Relevant preliminary data:

Our technique requires specific rectifications of the positive model which we have quantified using rectification mapping (Figure 1).

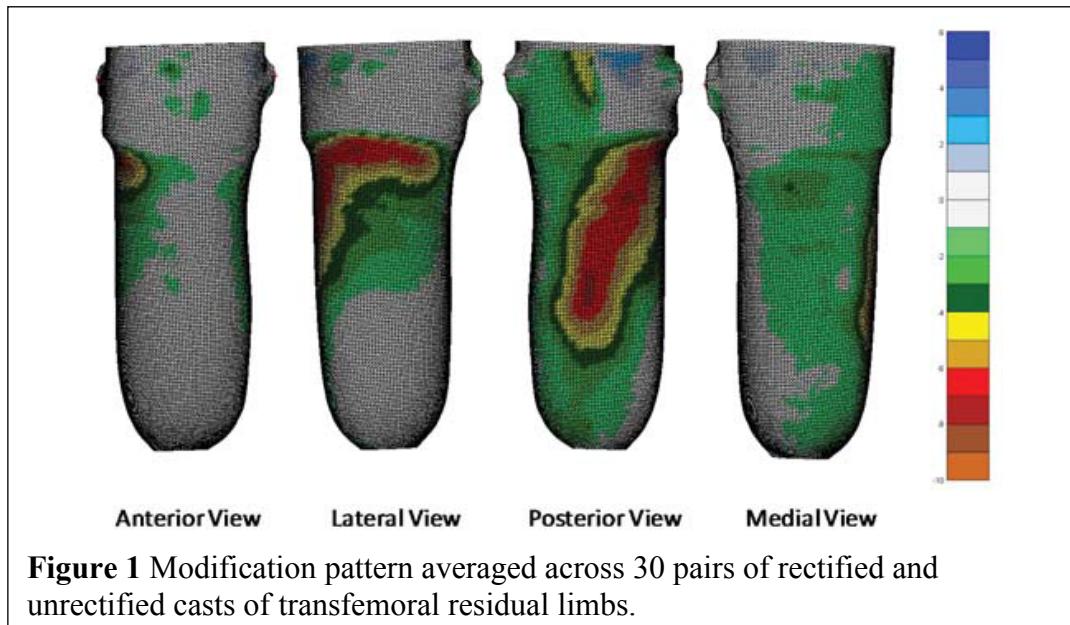


Figure 1 Modification pattern averaged across 30 pairs of rectified and unrectified casts of transfemoral residual limbs.

Preliminary tests of individuals using sub-ischial sockets illustrate that they do not use significant trunk lean during walking (Figure 2).

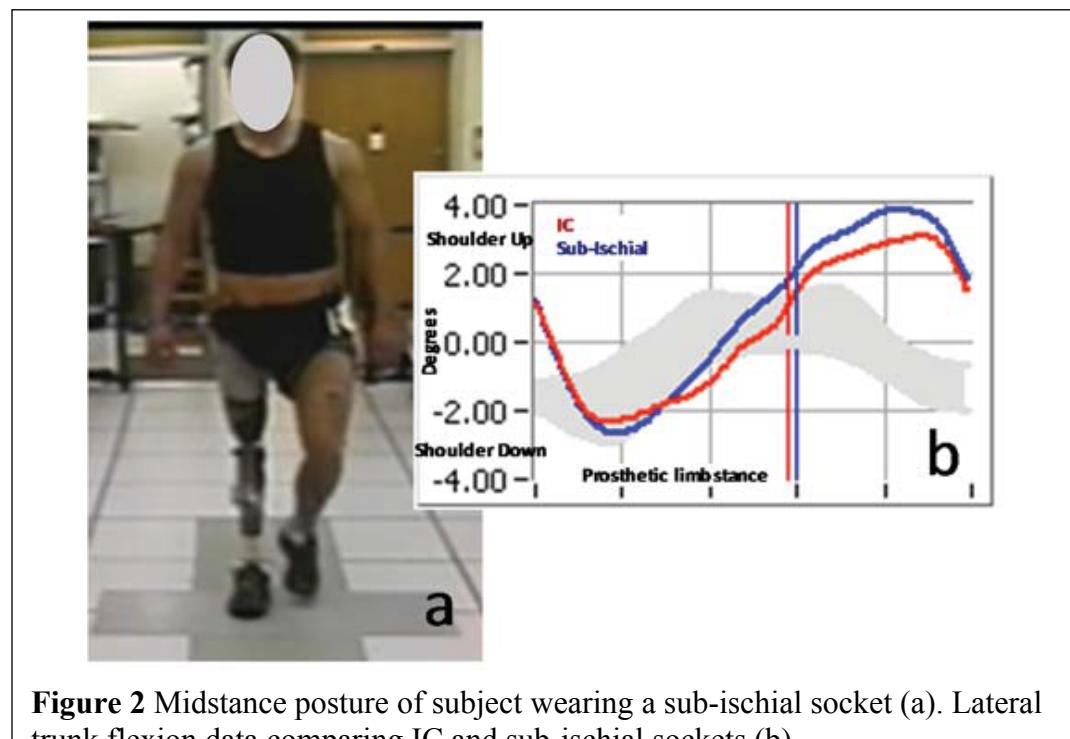


Figure 2 Midstance posture of subject wearing a sub-ischial socket (a). Lateral trunk flexion data comparing IC and sub-ischial sockets (b).

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We recently described the relationship between IC, tissue loading and socket comfort (Fatone, Dillon et al. 2015). Using a small randomized cross-over trial, it was shown that with the ischium contained, tissue loading did not influence socket comfort. Sockets without IC required high tissue loading to be as comfortable as those with IC, while suboptimal tissue loading compromised comfort.

The objective of our FY09 PRORP Technology Development Award from DOD was to develop a highly flexible sub-ischial prosthetic socket with vacuum-assisted suspension for highly active persons with transfemoral amputation. Hence, we used engineering analysis to characterize the socket, explored advanced manufacturing approaches for socket fabrication, characterized the function of commercially available vacuum pumps, designed and tested a hybrid mechanical/electrical pump, quantified the process of socket rectifications, and developed education materials to help teach this technique to other prosthetists. Additionally, preliminary evaluation of the NU-FlexSIV Socket with highly active persons with unilateral transfemoral amputation is underway at the Center for the Intrepid/Brooke Army Medical Center. To date, five of the six subjects we plan to test have been recruited for the study, with one subject having completed the entire protocol and four in process. At this point, subjects' responses indicate that they prefer the NU-FlexSIV Socket to their usual IC socket. One common benefit reported was the ability to sit without the socket beneath the ischium. Objective outcome measures likewise support the superiority of the NU-FlexSIV Socket. Data from the first subject to complete the full testing protocol (Figure 3) showed that the NU-FlexSIV Socket resulted in 10° greater active peak hip flexion, 13° greater active peak hip extension and 9° more hip abduction; sit-to-stand time improved by almost 2 seconds; hip range of motion increased 20.6°; T-Test performance improved by 4 seconds (16%). Across 5 walking trials, hip range of motion increased $12.5 \pm 1.2^\circ$ with the NU-FlexSIV Socket and the hip was able to achieve extension during walking. Additional case data from two non-military persons with transfemoral amputation is consistent with these findings.

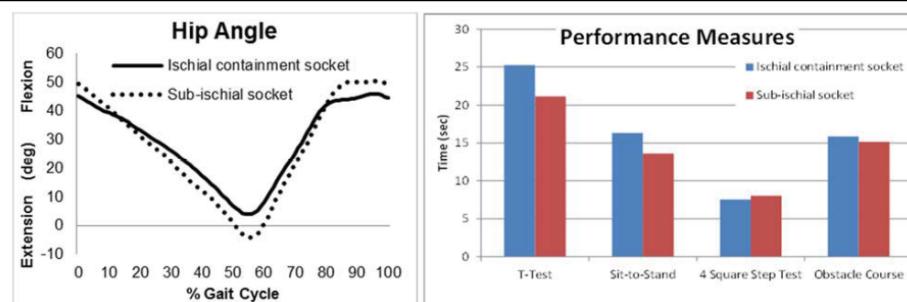


Figure 3 Performance data from first subject to complete testing.

2.3 Scientific or scholarly background for rationale and significance of the research:

To our knowledge, only one other group has demonstrated the efficacy of brimless (i.e., subischial) sockets for persons with transfemoral amputation (Kahle

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and Highsmith 2013, Kahle and Highsmith 2014). Using a small (n=10) randomized cross-over trial, gait and balance were found to be equivalent between sockets (IC and brimless) but subjects preferred the brimless socket. In this case, it appears that a rigid IC socket with a flexible brim was cut down to form the brimless socket. Similar improvements in comfort along with better functional outcomes may occur with sockets that are deliberately designed to be subischial, such as the NU-FlexSIV Socket.

3.0 Inclusion and Exclusion Criteria

3.1 Screening for eligibility:

Subjects interested in participating in this study will be screened for eligibility against the inclusion/exclusion criteria by one of the Certified Prosthetists through a clinical exam that assesses the status of the residual limb and walking ability.

3.2 Criteria that define who will be included or excluded in the study:

To participate in the study subjects must:

- be older than 21 years,
- have a unilateral transfemoral amputation,
- have used a prosthesis for two or more years,
- have a residual limb that is stable in volume and free from any wounds,
- be physically fit enough to participate in the performance tests, effectively making them a Medicare Functional Classification Level of K3 (the ability or potential for ambulation with variable cadence - a typical community ambulator with the ability to traverse most environmental barriers and may have vocational, therapeutic, or exercise activity that demands prosthetic use beyond simple locomotion) or K4 (the ability or potential for prosthetic ambulation that exceeds basic ambulation skills, exhibiting high impact, stress, or energy levels - typical of the prosthetic demands of the child, active adult, or athlete),
- have no previous experience of the sub-ischial socket, and
- be expected to be able to complete all visits for the duration of the protocol.

Subjects will be excluded if:

- they have a residual limb femur of less than 5 inches,
- present with any other co-morbidities that affect function, including neurologic abnormalities, e.g. neuropathic pain that would interfere with the study, and/or
- they do not speak and read English.

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3.3 Individuals from the following populations will be excluded:

- Adults unable to consent
- Individuals who are not yet adults (infants, children, teenagers)
- Pregnant women
- Prisoners

4.0 Study-Wide Number of Subjects

4.1 Total number of subjects to be accrued across all sites for multi-site trial:

N/A

5.0 Study-Wide Recruitment Methods

5.1 When, where, and how potential subjects will be recruited:

A convenience sample of participants will be recruited primarily by referral of prosthetists in the Chicago-land area. We will recruit both Veteran and non-Veteran subjects to participate in this study. With the assistance of Dr. Marc Applebaum, chief of Physical Medicine and Rehabilitation at the Jesse Brown VA Medical Center we will identify and recruit Veterans with unilateral transfemoral amputation. Non-Veteran participants will be recruited from the general community with the assistance of our clinical collaborators at Scheck & Siress Prosthetics, Orthotics and Pedorthics, the largest provider of orthotic and prosthetic clinical care in the Chicagoland area with over 40 certified and licensed orthotic and prosthetic practitioners and twelve accredited facilities.

As a secondary source of recruitment, information about the study will be circulated to other prosthetists in the midwest via the Midwest Chapter of the American Academy of Orthotists and Prosthetists, whose members include prosthetists practicing in Illinois, Indiana and Wisconsin; via amputee support groups and amputee sporting groups in the Chicago land area; as well as via the NUPOC and Scheck & Siress websites and facebook pages.

5.2 Methods to be used to identify potential subjects:

Subjects will be identified primarily by referral from local area prosthetists.

5.3 Materials used to recruit subjects:

Study flyer included in eIRB+ application.

6.0 Multi-Site Research

6.1 Processes to ensure communication among sites for multi-site study:

N/A

6.2 Method for communicating with participating sites:

N/A

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7.0 Study Timelines

7.1 Duration of an individual subject's participation in the study, duration anticipated to enroll all study subjects, estimated date for the investigators to complete primary analyses:

- Subjects will participate in this study for approximately 14 weeks (Figure 4).
- It is anticipated that we will recruit 10 subjects per year for each of the first 3 years and 5 subjects in the 4th year of the clinical trial.
- Data will be processed and analyzed for the final subject in month 33

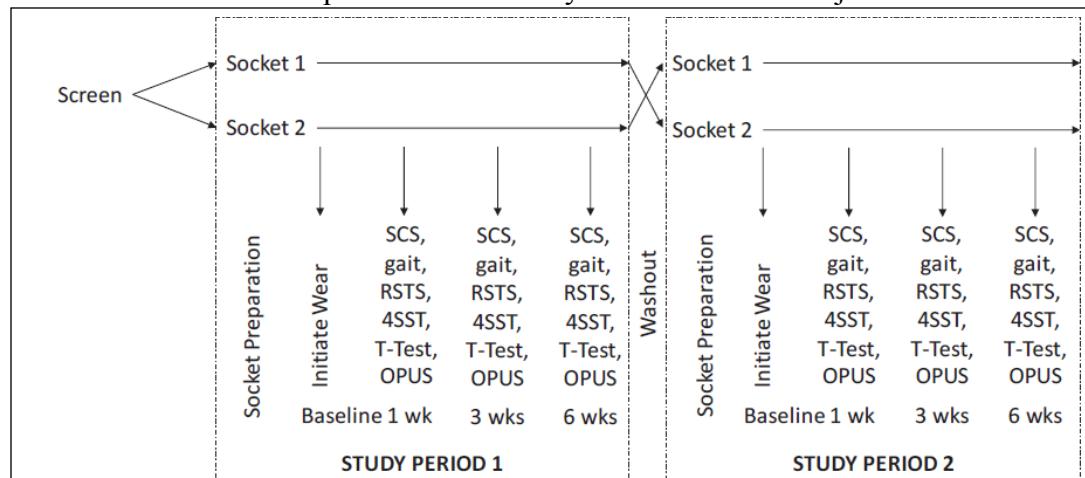


Figure 4 Study design and protocol.

of the study.

8.0 Study Endpoints

8.1 Primary and secondary study endpoints:

Our primary end point, socket comfort, will be assessed using the Socket Comfort Score (Hanspal, Fisher et al. 2003) an ordinal scale where 0 = the most uncomfortable socket fit imaginable and 10 = the most comfortable socket fit. Poor socket comfort is one of the most common issues experienced by prosthesis users. Like pain, comfort is subjective and difficult to measure. Therefore, pain-measurement methods such as the numerical rating scale (NRS) were used as models for quantifying and communicating socket comfort. The Socket Comfort Score asks the standard question, “On a 0 to 10 scale, 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?”

Our secondary end point, functional performance, will be assessed using instrumented motion analysis to record biomechanics of walking at different speeds, a 5-time Rapid Sit-to-Stand Test (RSTS), Four-Square-Step Test (FSST), and T-test of Agility. The 5-time Rapid Sit-to-Stand Test, Four-

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Square-Step Test, and T-test of Agility are standardized clinical measures of performance. We will also assess patient reported functional performance, quality of life and satisfaction with device using the Orthotic and Prosthetic Users' Survey (OPUS) (Heinemann, Bode et al. 2003).

8.2 Primary or secondary safety endpoints:

N/A

9.0 Procedures Involved

9.1 Study design:

The clinical trial will be an assessor-blinded prospective randomized cross-over trial wherein participants with unilateral transfemoral amputation will be randomized to using one of two socket conditions (i.e., sub-ischial or ischial containment) before crossing over to the other socket condition. Random allocation (computer-generated) utilizing blocks of random size will be used to assign the initial treatment condition. The trial will be balanced such that all subjects will receive all treatments (i.e., both socket conditions) and that all subjects will participate for the same number of periods (i.e., two).

9.2 Research procedures:

The study is composed of two phases for each socket: socket preparation and then 6 weeks of socket wear during which 3 identical data collection sessions will be held (week 1, 3 weeks and 6 weeks).

Socket Preparation Phase:

All sockets will be made following standard clinical procedures that include taking an impression (i.e., cast) of the residual limb, converting the negative residual limb model to a positive mold made of plaster of Paris, rectifying the positive mold using the rectification procedures specific to each socket design, thermoforming a clear diagnostic check socket, and ultimately manually fabricating, fitting and aligning a definitive socket.

Data Collection:

At each visit we will collect the following data:

1. *Socket Comfort Score (SCS)* – The SCS is a simple rating of comfort on a scale of 0 to 10 where 0 is the most uncomfortable socket fit imaginable and 10 is the most comfortable socket fit.
2. *Orthotic and Prosthetic Users' Survey (OPUS)* – The OPUS is a set of surveys that evaluate the subject's perception of function, quality of life, and satisfaction with the socket and prosthesis. The lower extremity function survey has 20 questions rated on a 5-point scale; the quality of life survey has 23 questions rated on a 5-point scale; and the satisfaction with device survey has 9 questions rated on a 5-point scale.

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3. *Biomechanics of Walking* – How the subjects walks with each socket will be measured in a computerized motion analysis lab. Small reflective markers are taped to anatomical landmarks on the legs, pelvis and arms using hypoallergenic tape. The subject then walks back and forth at their own comfortable walking speed while cameras on the wall record where the reflective markers are in space and force plates mounted flush in the floor measure the force applied by each foot.
4. *5-Time Rapid Sit-to-Stand Test (RSTS)* - The RSTS measures hip range of motion, lower limb muscle strength, and balance. The test involves measuring the time it takes for the subject to stand up and sit down five times with their arms folded across their chest as fast as they can. They will do this test twice with 3 minutes of rest in between each test.
5. *Four-Square-Step Test (FSST)* - The FSST evaluates dynamic standing stability and involves rapid stepping in different directions over an obstacle. The obstacle consists of a square cross made by resting four sticks flat on the floor. A stepping pattern is demonstrated to the subject and then one practice trial is allowed to ensure that they understand the pattern. They must try to complete the stepping pattern as fast as possible without touching the sticks. Both feet must make contact with the floor in each square. If possible, the subject must face forward during the entire test. They will do this test twice with 3 minutes of rest in between each test.
6. *T-Test of Agility (T-Test)* - The T-Test is typically used by athletes to test movement agility. Four markers are set out on the floor in the shape of a T. The subject starts at the marker located at the bottom of the T. When the investigator says “go” the subject moves forward as fast as they can to touch the second marker, they then shuffle sideways to the right to touch the third marker, and then they shuffle to the left, past the second marker, to touch the fourth marker. The subject then shuffles back to their right to touch the second marker and then moves backwards as fast as they can to touch the first marker. The test is timed and should be performed as fast as possible. The test is repeated three times and the best time is used. The subject will be allowed to rest for 3 minutes between tests.

9.3 (a) Procedures performed to lessen the probability or magnitude of risks:

All socket fabrication procedures used in this study are consistent with standard clinical care procedures. The standard clinical process of making a transfemoral prosthetic socket involves some loss of modesty and privacy given the intimate fit of the standard-of-care Ischial Containment socket with your groin and buttocks. Certified Prosthetists are trained to ensure privacy during this process. Risk is further minimized by recruiting subjects who have used a prosthesis for at least two years and are therefore familiar with the process.

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It is possible that one or both sockets may not be comfortable or that one or both sockets may rub the residual limb and cause redness, blistering, or a sore, just as any new or ill-fitting socket may do. Inclusion/exclusion criteria will help minimize the risk of these problems by only allowing persons to participate who have used a prosthesis for at least two years, have a residual limb that is stable in volume and free from any wounds and no skin/residual limb issues that make fitting a socket problematic. Subjects will actively contribute to minimizing residual limb problems by checking their limb each day, informing investigators of problems as soon as they occur, and working with the study prosthetists to resolve any issues.

Transfemoral amputees are generally at greater risk for stumbling, tripping and falling than people who are not amputees. The risk of stumbling, tripping and falling may be increased while performing some of the mobility tests used in this study. All tests are standardized clinical outcome measures used with amputees and will be performed under controlled lab conditions to ensure that the subject is not distracted from the task and that all other conditions such as ambient lighting, floor surfaces, etc. are favorable, helping minimize risk. Subjects are asked to perform some of the tests “as fast as they can” rather than pushing them to exceed their own comfortable limits, further serving to minimize risk.

(b) Devices used in this research, the purpose of their use, and their regulatory approval status:

Two designs of custom made prosthetic sockets will be compared in this research: (1) the Ischial Containment (IC) Socket and (2) the NU-FlexSIV Socket (Figure 5).

The standard-of-care IC socket design will be determined on a per-subject basis by the Certified Prosthetist using standard clinical practice procedures. However, subject selection criteria will serve to decrease the variability in patient presentation such that it will minimize the choice of suspension options. Therefore, the IC socket will consist of a flexible inner socket with rigid frame using either skin fit suction suspension with a one way valve or silicon liner with locking mechanism. If a liner is used it will be sized according to manufacturer recommendations.

The NU-FlexSIV Socket will also be custom fit to each subject using standard clinical practice procedures. Subischial socket trim lines are typically 25mm distal to the ischial tuberosity and 50mm distal to the greater trochanter and while it also has a narrower medio-lateral than



Figure 5 Ischial Containment Socket (left) and NU-FlexSIV Socket (right).

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anterior-posterior dimension, it has a more rounded cross-sectional profile than the IC socket. All subjects will be fit with an undersized liner (i.e., liner one size smaller than the manufacture recommendation based on measurements) over which the sub-ischial socket will be fitted. Using the rectification procedures specific for this design, sockets are also 4-6% undersized. Suspension will be achieved using an Össur Unity mechanical vacuum pump.

With the exception of the prosthetic foot, prosthetic components distal to the socket (the knee and pylon) will be standardized within subjects. Subjects will use their current prosthetic knee so as to minimize the burden of learning to walk with a different knee. All subjects will be provided an Össur LP Variflex foot with Unity Pump to wear with both test sockets. This foot is suitable for K3 and K4 ambulators⁵² and can interface with any existing componentry while also providing a noiseless vacuum pump for use with the sub-ischial socket condition.

The purpose of both sockets is to restore the ability to walk for someone with a transfemoral amputation. Prosthetic sockets form the interface between the residual limb and prosthesis, allowing for support of body weight and transfer of forces between the amputee and the prosthesis.

The type of external limb prosthesis we propose to evaluate as part of this clinical trial is considered by the Food and Drug Administration (FDA) as a Class I device (low risk) and 510k exempt (although not necessarily IDE exempt). As part of our current IRB approval for a pilot study with the same device (STU00033446), a determination was made by the FDA that our device was not a custom device, necessitating that the Northwestern University Institutional Review Board (NU-IRB) make a significant risk determination. The NU-IRB made a determination that the use of the device constituted a non-significant risk, which meant that we did not have to apply for an Investigational Device Exemption from the FDA.

According to FDA regulation 21CFR890 (External Limb Prosthetic Component) our device meets that requirement but does not have an automatic exemption. Hence, whether our device is subject to FDA regulation for this proposed work depends upon NU-IRB determination of whether the device as proposed for use in this study is a significant risk device. If the NU-IRB determines as it did previously for a similar smaller pilot study that our device constitutes a non-significant risk, then we will not be subject to FDA regulation and will not need to apply for an IDE.

According to FDA requirements, as the manufacturer of the device, the Principal Investigator (PI) can make the determination that this is a non-significant risk device. The subsequent IRB determination will either support the PI's decision or override it and require that an IDE application be submitted to the FDA. Hence, based on previous experience regarding FDA and IRB determinations and recent correspondence with NU-IRB regarding this issue (see attached), the PI has determined that the device to

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be used in this study constitutes a non-significant risk and hence an IDE is not required and has not been applied for. We are aware that this determination is subject to change based on review by NU-IRB.

(c) Source records that will be used to collect data about subjects:

All data needed for this study will be collected directly from the subjects. Included in the eIRB+ application are the Subject Information Form, Socket Measurement Forms, OPUS and AMP data collection forms.

9.4 Data to be collected:

- *Patient Characteristics:* age, height/weight, time since amputation, etiology of amputation, residual limb length, residual limb tissue type (soft, medium, firm), hip flexion contracture magnitude, current prosthesis description, Socket Comfort Score in existing socket, and Medicare Functional Classification Level assessed using the Amputee Mobility Predictor (AMP).
- *Socket Measurements:* See Socket Measurement Forms in eIRB+ application.
- *Patient-Reported Outcomes:* Socket Comfort Score and OPUS.
- *Functional Performance Measures:* biomechanics of gait, 5-times Rapid Sit-to-Stand Test, Four Square Step Test, T-Test of Agility.

9.5 For HUD uses provide a description of the device, a summary of how you propose to use the device, including a description of any screening procedures, the HUD procedure, and any patient follow-up visits, tests or procedures:

N/A

10.0 Data and Specimen Banking

10.1 Data or specimens banking for future use:

Specimens are not applicable.

The investigators will retain all data recorded during the study. Any electronic data maintained at NUPOC is on encrypted and password protected computers in locked rooms and paper files are stored in locked cabinets in locked rooms. Both computers and paper files are accessible only to NUPOC personnel. Data will not be destroyed.

De-identified data will be entered into RedCap for analysis by the statistician.

10.2 Data to be stored or associated with each specimen:

N/A

10.3 Procedures to release data or specimens:

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N/A

11.0 Data and Specimen Management

11.1 Data analysis:

Before analyses begin, all variables will be plotted using histograms to inspect the shape of distributions and to check for outliers. We will not drop cases nor transform variables but if we identify any possibility that assumptions have been violated, we will employ alternative analysis approaches. As part of data screening, we will describe the amount of data that are missing, and we will compare participants with and without missing data.

Hypothesis 1: We hypothesize that the NU-FlexSIV Socket will provide increased comfort compared to the ischial containment socket.

Our primary end point is Socket Comfort Score at 6 weeks, which has been reported to have a sensitivity to socket change of 1 to 3 points (Hanspal, Fisher et al. 2003). Additionally, it has been argued that the Socket Comfort Score may be considered a continuous variable, and therefore suitable for parametric analysis, given the large number of ordered categories and the linear nature of changes in socket comfort with different configurations of socket conditions (Fatone, Dillon et al. 2015). Hence, a matched pairs t-test ($\alpha=0.05$) will be used to assess the primary outcome, Socket Comfort Score.

Hypothesis 2a: We hypothesize that the NU-FlexSIV Socket will allow greater prosthetic side hip range of motion, in particular increased hip extension, leading to increased prosthetic side step length and hence walking speed compared to the ischial containment socket.

Hypothesis 2b: We hypothesize that step width and lateral trunk flexion over the prosthetic limb will not differ between the NU-FlexSIV Socket and ischial containment socket.

For these secondary hypotheses, data analysis will include the following gait variables: walking speed (m/s), step width (m), step length (m), sagittal plane hip range of motion (degrees), maximum hip extension (degrees), and lateral trunk lean over the prosthetic limb during stance (degrees). A multiple analysis of variance (MANOVA, $\alpha=0.05$) will be used to compare gait variables across socket conditions as it is the most rigorous approach given the relationship that exists between these dependent variables (e.g., walking velocity and step length are correlated). The challenge of this approach is being convinced that underlying assumptions are met.

Hypothesis 2c: We hypothesize that the NU-FlexSIV Socket will result in faster times to perform the 5-Times Rapid Sit-to-Stand Test, Four Square Step Test and T-Test of Agility compared to the ischial containment socket.

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The difference in these timed performance tests across socket conditions will be tested using repeated measures t-tests with alpha=0.05 which will be adjusted using the Bonferroni correction to account for Type 1 error.

Hypothesis 3: We hypothesize that the NU-FlexSIV Socket will result in better health-related quality of life and satisfaction with device as assessed using the OPUS compared to the ischial containment socket.

The OPUS uses Likert scale responses for each item of each module. However, these responses can be converted into a single score for each module. If assumptions of normality are met, analysis with parametric procedures can be used to assess differences in module scores between sockets. Hence, we will use repeated measures t-tests with alpha=0.05 which will be adjusted using the Bonferroni correction to account for Type 1 error.

11.2 Power analysis:

To determine a sample size estimate, we have utilized data obtained from a previous pilot study.⁴⁴ In that study, we collected Socket Comfort Scores from six persons with unilateral transfemoral amputation wearing an ischial ramal containment socket and the same socket with a wider medio-lateral dimension (effect size, $d = 0.754$). Using the G*Power computer program, this effect size was used to estimate sample size. This data was used because we do not have pilot data for this particular study design. For a 2-tailed matched pairs t-test we would need a total sample size of 25 to detect an effect size of 0.754 with a critical alpha of 0.05 and power of 0.95. In order to account for possible attrition in subject numbers we will recruit 35 persons with unilateral transfemoral amputation.

11.3 Steps to be taken to secure the data to maintain confidentiality during storage, use, and transmission:

All personnel involved with the study have or will complete IRB required training.

Subjects will be assigned a study code at enrollment and all study related forms to be completed by our clinical collaborators will be labelled only with the study code. Forms that require the subject's identity and cannot be coded (e.g. payment paperwork) will only be completed at NUPOC and not at the clinical sites. The master list of study codes will be maintained at NUPOC by the PI. This master list will only be maintained in hard copy format, in a locked cabinet in the PI's office which is also locked.

The collaborating prosthetists will only create and use the forms required for recording the fitting and fabrication of their particular socket and these can be de-identified. Once the subject has completed that phase of the study, forms are given in person or by mail to the PI to collate with the main subject file to be held at NUPOC.

All electronic data maintained at NUPOC is on encrypted and password protected computers located in locked rooms and all paper files are stored in

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locked cabinets in locked rooms. Both computers and paper files are accessible only to NUPOC personnel.

All data entered into RedCap will be de-identified summary data needed for statistical analysis.

11.4 Procedures to be used for quality control of collected data:

A cross-over study has two advantages over both parallel and non-crossover longitudinal study designs. First, the influence of confounding covariates is reduced because each cross-over patient serves as their own control. This is particularly important given the custom nature of prosthetic interventions. Second, cross-over designs can be statistically efficient, requiring fewer subjects than non-cross-over designs. This is of particular benefit for prosthetic studies given the cost, time and effort involved in providing custom prosthetic devices for use every day during the study. Cross-over studies are typically subject to order effects, which in this case the most likely is shrinking of the residual limb during the first intervention phase. This shrinkage is typical of what happens any time a new, more tightly fitting socket is provided to a person with amputation. However, the effect of shrinkage is accounted for by having casting and fabrication of the second test sockets occur after data collection in the first socket is completed. While a washout period is not strictly necessary, it is effectively included as subjects will need to transition back to their usual, pre-study socket/prosthesis while the second test socket is fabricated.

Socket allocation will be concealed from the investigators until after a subject is enrolled. The starting socket design will be enclosed in sequentially numbered, opaque, sealed envelopes. Envelopes will be opened sequentially and only after the participant's name and other details are written on the appropriate envelope.

Blinding of prosthetic interventions is challenging given that they are devices that must be custom-fabricated and donned each day by the subject. Hence, for this study only the assessor, our research engineer, Ms Lilly Tran, will be blinded. To maintain blinding the assessor will remain uninformed in any aspect of the study except administration of performance and patient-reported measures and processing motion analysis data.

- The assessor will not be present for motion analysis data collection given that this requires exposure of the prosthesis and socket for appropriate marker placement. Since all that is recorded is the location of retro-reflective markers on the subject, it is not

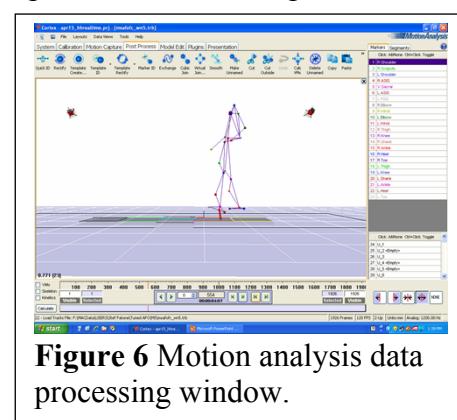


Figure 6 Motion analysis data processing window.

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possible to tell while processing the motion analysis data what socket the subject was wearing because the data is viewed only as a stick figure (Figure 6).

- Performance and patient-reported measures can be administered fully clothed, which will disguise the socket being tested. During these assessments, subjects will be instructed not to reveal to the assessor which socket they are wearing.

Given the customized, manually-fabricated nature of prosthetic sockets, each test socket will be provided to study subjects by a separate Certified Prosthetist known for their skill with the particular socket design. This will ensure that each socket is the best and most consistent example of each particular socket design.

Since accommodation to sockets is unknown, data will be collected at baseline (within one week of definitive socket fitting) and after 3 and 6 weeks of every day socket use. These time points were chosen to enhance subject retention. Since we anticipate that one socket will be more comfortable than the other, it is possible that some subjects will find it challenging to use the less comfortable socket for a long period of time. By keeping each testing phase reasonably short (i.e., 6 weeks) we hope to retain as many subjects as possible. Additionally, by collecting data at 3 time points, we hope that if subjects are unable to continue to wear the socket for the entire six weeks, we will have initial and intermediate times points for comparison.

Step activity monitors attached to the test prostheses will allow monitoring of every day socket use. This will provide information regarding compliance with use of each prosthesis. As a secondary consideration, it will allow us to check whether there is a relationship between comfort and step activity.

When assessing the biomechanics of walking data consistency will be assured by (1) collecting all data in the same laboratory using the same instrumentation; (2) having marker placement conducted by the same experienced person who has been shown previously to have high reliability in this task; and (3) having a single person post-process all the data.

Since we hypothesize that the sub-ischial socket will be more comfortable than the standard-of-care ischial containment socket, it may be difficult to convince current wearers of the sub-ischial socket to revert to wearing an ischial containment socket every day for the time required by the study. It is also likely that those who have already adopted the sub-ischial socket will be particularly biased against the ischial containment socket, leading to larger differences in our primary endpoint. To account for this issue, we plan to recruit only those patients with no previous experience of the sub-ischial socket.

11.5 Handling of data study-wide:

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Any electronic data maintained at NUPOC is on encrypted and password protected computers located in locked rooms and all paper files are stored in locked cabinets in locked rooms. Both computers and paper files are accessible only to NUPOC personnel.

The collaborating prosthetists will only create and use the forms required for recording the fitting and fabrication of their particular socket and these can be de-identified. Once the subject has completed that phase of the study, forms are given in person or by mail to the PI to collate with the main subject file to be held at NUPOC.

Data will be retained indefinitely. There are no plans to destroy the data.

12.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

N/A

13.0 Withdrawal of Subjects*

13.1 Anticipated circumstances under which subjects will be withdrawn from the research without their consent:

The PI can remove subjects from the research study without their approval if they fail to regularly attend study visits, fail to communicate about socket and residual limb problems, and fail to work with the prosthetists to resolve socket fitting or residual limb issues.

13.2 Procedures for orderly termination:

If the above circumstances occur, the PI will contact the subject to advise them that their participation in the research is being terminated. Depending on what phase of the study the subject is in, the PI will need to organize for the subject to receive their regular prosthesis back intact. This is required because the study prosthetist must place the subject's prosthetic knee back into their regular prosthesis.

13.3 Procedures to be followed when subjects withdraw from the research:

If subjects decide to leave the research, they must contact the investigator so that the investigator can arrange for their regular prosthesis to be returned to them intact. This requires that the study prosthetist place their prosthetic knee back into their regular prosthesis.

14.0 Risks to Subjects*

14.1 Foreseeable risks, discomforts, hazards, or inconveniences to the subjects related the subjects' participation in the research:

Participating in this study will expose subjects to many of the same risks as you are regularly exposed to as an above-the-knee prosthesis user.

(1) The standard clinical process of making a transfemoral prosthetic socket involves some loss of modesty and privacy given the intimate

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fit of the standard-of-care Ischial Containment socket with the groin and buttocks. This is a temporary situation that occurs primarily during the socket preparation phase of the study.

(2) It is possible that one or both sockets may not be comfortable or that one or both sockets may rub the residual limb and cause redness, blistering, or even a sore, just as any new or ill-fitting socket may do. Regular inspection of the residual limb by the subject at the end of each day will help identify red spots and blisters before they become sores. Immediate communication of these issues to the study investigators and prompt action by the study prosthetist can help minimize the likelihood that red spots become sores.

(3) As transfemoral amputees, all subjects are at greater risk for stumbling, tripping and falling than people who are not amputees. Additionally, the risk of stumbling, tripping and falling may be increased while performing some of the mobility tests used in this study.

14.2 Procedures that may have risks to the subjects that are currently unforeseeable:

N/A

14.3 Procedures that may have risks to an embryo or fetus should the subject be or become pregnant:

N/A

14.4 Risks to others who are not subjects:

N/A

15.0 Potential Benefits to Subjects

15.1 Potential benefits that individual subjects may experience from taking part in the research. Include as may be useful for the IRB's consideration, the probability, magnitude, and duration of the potential benefits:

Possible benefits that individual subject's may experience from participating in this research include (1) contributing to the development of evidence to support whether or not the new socket design is more comfortable and functional than the current standard-of-care transfemoral socket; and (2) receipt of one or two new sockets.

Since the sockets made for this study are made to uniquely fit individual subjects, they will be allowed to keep either or both sockets assuming they fit well. Sockets will be provided to the subject at the end of the study to take to their regular prosthetist who can work with them if they want to continue wearing one of the sockets.

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15.2 Indicate if there is no direct benefit:

N/A

16.0 Vulnerable Populations

16.1 If the research involves individuals who are vulnerable to coercion or undue influence, describe additional safeguards included to protect their rights and welfare:

N/A

17.0 Community-Based Participatory Research

17.1 Involvement of the community in the design and conduct of the research:

N/A

18.0 Sharing of Results with Subjects

18.1 Sharing of results with subjects or others:

Results will not be shared with subjects or others.

19.0 Setting

19.1 Sites where the research team will conduct the research:

The research team will identify and recruit potential subjects: A convenience sample of participants will be recruited primarily by referral of prosthetists in the Chicago-land area. We will recruit both Veteran and non-Veteran subjects to participate in this study. With the assistance of Dr. Marc Applebaum, chief of Physical Medicine and Rehabilitation at the Jesse Brown VA Medical Center we will identify and recruit Veterans with unilateral transfemoral amputation. Non-Veteran participants will be recruited from the general community with the assistance of our clinical collaborators at Scheck & Siress Prosthetics, Orthotics and Pedorthics, the largest provider of orthotic and prosthetic clinical care in the Chicagoland area with over 40 certified and licensed orthotic and prosthetic practitioners and twelve accredited facilities.

As a secondary source of recruitment, information about the study will be circulated to other prosthetists in the midwest via the Midwest Chapter of the American Academy of Orthotists and Prosthetists, whose members include prosthetists practicing in Illinois, Indiana and Wisconsin.

Research procedures will be performed at NUPOC and at Scheck and Siress Prosthetics, Orthotics and Pedorthics. NUPOC includes the Jesse Brown VA Medical Center Motion Analysis Research Laboratory.

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VA regulations will apply for Veterans who may participate in the study, however there are no site-specific regulations or customs at Scheck & Siress.

Approval for recruitment of Veteran subjects will be sought from the Jesse Brown VA Medical Center IRB. Scheck & Siress do not have an IRB of their own, so NU IRB will be the presiding authority.

20.0 Resources Available

20.1 Qualifications of study team:

The clinical team is headed by Principal Investigator, Stefania Fatone, PhD, BPO(Hons). Dr. Fatone is a prosthetist/orthotist with nearly 20 years of experience conducting biomechanical research, including small clinical studies based on gait analyses of persons who use prostheses and orthoses. Dr. Fatone has completed all NU and VA IRB required training for human subject research.

Dr. Thomas Schnitzer, MD/PhD, has extensive experience in design and implementation of clinical trials and will work closely with the PI to provide guidance and advice on the conduct and management of the current clinical trial. Dr. Schnitzer has completed all IRB required training for human subject research.

Ryan Caldwell, CP, and John Angelico, CP, both Certified Prosthetists, will be responsible for each of the prosthetic sockets to be tested in this study. Mr. Caldwell is the originator of the NU-FlexSIV Socket and has extensive experience providing this socket technology successfully as part of his prosthetic clinical practice at Scheck & Siress Prosthetics, Orthotics and Pedorthics. Mr. Angelico has over 30 years of experience as an American Board Certified and Illinois Licensed Prosthetist and is an examiner for the American Board for Certification in Prosthetics, Orthotics and Pedorthics. Mr. Caldwell has completed all IRB required training for human subject research and Mr. Angelico is currently undertaking training.

Dr. Steven Gard, PhD, is both faculty at Northwestern and a VA Research Health Scientist. He will be responsible for managing allocation of interventions and ensuring that other investigators are unaware of allocation until after a subject is enrolled in the study. He will also assist with recruitment of Veteran subjects and manage VA IRB requirements. Dr. Gard has completed all NU and VA IRB required training for human subject research.

Dr. Marc Applebaum, MD, chief of Physical Medicine and Rehabilitation at the Jesse Brown VA Medical Center, will identify and recruit Veterans with unilateral transfemoral amputation at the Jesse Brown VA Medical Center.

Rebecca Stine, MS, is the Manager of the Jesse Brown VA Medical Center Motion Analysis Research Laboratory located at NUPOC. Ms. Stine has nearly 30 years of experience in the use of instrumented motion analysis.

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Ms. Stine will collect all gait data and contribute to the interpretation of the data. As manager, Ms. Stine is responsible for maintenance and operation of the JBVAMC-MARL facility and equipment. Ms. Stine has completed all NU and VA IRB required training for human subject research and serves on the new Jesse Brown VA Medical Center IRB.

Lilly Tran, MS, is a research engineer at the NUPOC who will assume the role of blinded assessor for this study. Ms. Tran has completed all IRB required training for human subject research.

Michael Oros, CPO, is President and CEO of Scheck & Siress and will help support implementation of the project at Scheck & Siress. Mr. Oros is currently undertaking training.

A statistician will be engaged to provide statistical support throughout the project.

20.2 Other resources available to conduct the research:

- Currently, about 1.9 million people are living with limb loss in the United States. A total of 19,864 lower limb amputation procedures were performed in the state of Illinois from 2009 to 2012. A total of 760 transfemoral amputation procedures were performed in 2012.
- We plan to recruit 10 subjects per year for the first 3 years of the clinical trial and 5 in the 4th year for a total of 35. These subjects will be a mix of civilians and Veterans. Given the size of the amputee population in Illinois and the scope of the clinical practice of our collaborators, we believe that this recruitment goal is feasible.
- The key personnel involved in this study will devote the equivalent of a day a week to this research project for the next three years.
- NUPOC is located on the Chicago campus of Northwestern University at 680 N. Lake Shore Drive, Suite 1100, Chicago, IL. NUPOC has a total of 20,000 sq. ft. of purpose designed space that is fully accessible to individuals with disabilities (i.e., no physical barriers are present which require any more than minimal effort to overcome). NUPOC includes a VA-sponsored research program under the auspices of the Jesse Brown VA Medical Center (JBVAMC). Hence, our research facilities include the Jesse Brown VA Medical Center Motion Analysis Research Laboratory (JBVAMC-MARL). JBVAMC-MARL is a 1200 sq. ft. state-of-the-art human movement research laboratory designed especially for making measurements necessary for characterizing human movements. Dr. Steven Gard is the director of the JBVAMC-MARL. JBVAMC-MARL is fully accessible to individuals with disabilities (i.e., no physical barriers are present which require any more than minimal effort to overcome).
- The Jesse Brown VA Medical Center (JBVAMC) provides care to approximately 58,000 enrolled veterans who reside in the City of Chicago and Cook County, Illinois, and in four counties in northwestern Indiana. JBVAMC is affiliated with the Feinberg School

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of Medicine of Northwestern University. The main hospital is located on the west side of Chicago at 820 S Damen Ave, Chicago, IL. A shuttle bus runs at regular intervals between the downtown medical campus of Northwestern University and JBVAMC, to facilitate interaction of patients, staff and research subjects between institutions. At JBVAMC, Dr. Marc Applebaum provides rehabilitation services and clinics for persons with amputation.

- Scheck & Siress is one of the most respected and well-established orthotic and prosthetic practices in the greater Chicagoland area. Founded in Oak Park, IL in 1953, Scheck & Siress is the largest provider of orthotic and prosthetic clinical care in the region, comprised of over 40 ABC Certified and Illinois Licensed orthotic and prosthetic practitioners and 12 ABC accredited facilities, including locations affiliated with Marianjoy Rehabilitation Center, University of Illinois (Chicago) Hospital, Rush University Medical Center, Northwestern Memorial Hospital, Ingalls Hospital, and Loyola University Medical Center.
- The study team will meet four times a year to discuss the project and ensure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions.

21.0 Prior Approvals

21.1 Approvals to be obtained prior to commencing the research:

Prior to participation of any human subjects, the approval of all required Institutional Review Boards (IRB) will be sought. This includes, umbrella study approval from the Northwestern University IRB, approval from the Jesse Brown VA Medical Center (JBVAMC) IRB, and administrative review and approval from the U.S. Army Medical Research and Materiel Command Office of Research Protections Human Research Protection Office (HRPO). Northwestern University will be the IRB of record for study related activity that takes place at Scheck & Siress. Additionally, prior to enrollment of the first subject, this clinical trial will be registered at clinicaltrials.gov.

22.0 Recruitment Methods

22.1 Recruitment of potential subjects:

A convenience sample of participants will be recruited primarily by referral of prosthetists in the Chicago-land area. We will recruit both Veteran and non-Veteran subjects to participate in this study. With the assistance of Dr. Marc Applebaum, chief of Physical Medicine and Rehabilitation at the Jesse Brown VA Medical Center we will identify and recruit Veterans with unilateral transfemoral amputation. Non-Veteran participants will be recruited from the general community with the assistance of our clinical collaborators at Scheck & Siress Prosthetics, Orthotics and Pedorthics, the

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largest provider of orthotic and prosthetic clinical care in the Chicagoland area with over 40 certified and licensed orthotic and prosthetic practitioners and 12 accredited facilities.

As a secondary source of recruitment, information about the study will be circulated to other prosthetists in the midwest via the Midwest Chapter of the American Academy of Orthotists and Prosthetists, whose members include prosthetists practicing in Illinois, Indiana and Wisconsin.

22.2 Source of subjects:

See 22.1.

22.3 Methods used to identify potential subjects:

See 22.1.

22.4 Materials that will be used to recruit subjects:

Study flyer included in eIRB+ application.

22.5 Amount, timing, and method of any payments to subjects:

Subjects will be paid \$100 per study visit up to a maximum \$1400. We will only pay for the study visits completed. Payment will be by check at the completion of the study. We will also provide discounted parking passes for the 222 Huron Street Parking Garage for the data collection visits that take place at NUPOC.

23.0 Local Number of Subjects

23.1 Total number of subjects to be accrued locally:

30

23.2 Break-down of subjects by study location or procedure group:

N/A

23.3 Number of subjects who are expected to be enrolled and screened, and the number of subjects needed to complete the research procedures:

We plan to enroll and screen 35 subjects and need 25 to complete the research.

24.0 Confidentiality

24.1 If this is a multicenter study, describe the local procedures for maintenance of confidentiality:

N/A

25.0 Provisions to Protect the Privacy Interests of Subjects

25.1 Steps to be taken to protect subjects' privacy interests:

Efforts will be made to limit the use and disclosure of subject's personal information, including research study and medical records, to people who

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have a need to review this information. However, we cannot promise complete secrecy. Organizations that may inspect and copy the subject's information include the IRB and other representatives of Northwestern University required to process various paperwork related to research (e.g. subject payment), the US Department of Defense (DOD), the DOD Human Research Protections Office, the Veterans Administration, and collaborators at Scheck and Siress Prosthetics, Orthotics and Pedorthics.

Subjects are required to interact with both study prosthetists, the motion analysis lab manager, the research engineer and the PI. This is the minimum interaction required to conduct the study. However, not all investigators need to have access to all the personal information collected as part of this project. The PI will work to compartmentalize the data collection forms such that only the information necessary for each study personnel to execute their study related tasks will be available.

25.2 Steps we will take to make the subjects feel at ease with the research situation:

The standard clinical process of making a transfemoral prosthetic socket involves some loss of modesty and privacy given the intimate fit of the standard-of-care Ischial Containment socket with your groin and buttocks. Certified Prosthetists are trained to ensure these activities take place in a private space. We are also recruiting subjects who have used a prosthesis for at least two years and are therefore familiar with the process as this will ease their experience of the study procedures.

25.3 Permission to access any sources of information about the subjects:

N/A

26.0 Compensation for Research-Related Injury

26.1 Describe the available compensation in the event of research-related injury.

N/A

26.2 Contract language relevant to compensation for research-related injury:

N/A

27.0 Economic Burden to Subjects

27.1 Costs that subjects may be responsible for because of participation in the research:

N/A

28.0 Consent Process

28.1 Process for obtaining consent:

We will follow "SOP: Written Documentation of Consent (HRP-091)."

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The consent process will take place at the end of screening or at the first study visit prior to beginning any study related procedures. The first study visit takes place at one of the Scheck & Siress clinical offices.

Subjects may have as much time as they like between being informed of the study and obtaining consent. Consent forms can be taken home for the subject for further perusal.

Non-English Speaking Subjects

N/A

Waiver or Alteration of Consent Process (consent will not be obtained, required information will not be disclosed, or the research involves deception)

N/A

Subjects who are not yet adults (infants, children, teenagers)

N/A

Cognitively Impaired Adults

N/A

Adults Unable to Consent

N/A

29.0 Process to Document Consent in Writing

29.1 How consent of the subject will be documented in writing:

We will follow “SOP: Written Documentation of Consent (HRP-091).”

29.2 Waiver of requirement to obtain written documentation of consent:

N/A

29.3 Consent document:

Consent document included in the eIRB+ application.

30.0 Drugs or Devices

30.1 Plans to store, handle, and administer devices:

Both prosthetic sockets are custom-made to fit the individual and as such no storage is needed and they cannot be used with other subjects as they won't fit.

30.2 Information about claim of an abbreviated IDE (non-significant risk device):

The PI of this study is the holder of the current abbreviated IDE. The type of external limb prosthesis we propose to evaluate as part of this clinical trial is considered by the Food and Drug Administration (FDA) as a Class I device (low risk). As part of our current IRB

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approval for a pilot study with the same device, a determination was made by the FDA that our device was not a custom device, necessitating that the Northwestern University Institutional Review Board (NU-IRB) make a significant risk determination. The NU-IRB made a determination that the use of the device constituted a non-significant risk, which meant that we did not have to apply for an Investigational Device Exemption from the FDA.

Our device can be classified as an external limb prosthetic component according to 21 CFR 890.3420. We believe that the NU-FlexSIV Socket like the standard-of-care Ischial Containment Socket meets the custom device definition as it is hand fabricated by the prosthetist for each subject using current clinical techniques. Given overwhelming similarities in structure between the NU-FlexSIV Socket and the standard-of-care Ischial Containment Socket we contend that the NU-FlexSIV Socket is a design variant of the type of sockets used safely every day by transfemoral amputees. Hence, we believe that our socket can be considered minimal risk.

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