Title: Personalizing MPK Prescription for Individuals with Transfemoral Amputation

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Protocol for Personalizing MPK Prescription for Individuals With Transfemoral Amputation

1. Study Aim, Background and Design

Background: Published data shows approximately 35% of service members who sustain an amputation have it occur at the transfemoral level. Significant evidence indicates microprocessor knees (MPKs) have numerous benefits over non-MPKs for individuals with transfemoral amputation (TFA) including improved gait, safety, comfort, confidence, reduced falls, balance, patient satisfaction and reduced energy expenditure, greater ease in negotiating varying terrains, improvements in multi-tasking and cost effectiveness, such that MPK technology should be considered current state-of-the-art in TFA prosthesis prescription. However, studies which currently exist on MPK technology tend to lump the various knees together as a group rather than teasing out differences between the individual MPK technology and what types of patients are best suited for each. Therefore, a gap exists in clinical knowledge forcing clinicians to choose componentry based on reimbursement or their past experiences with an MPK, rather than detailed evidence supporting the use of one MPK for a certain individual. In this proposal, we will assess the biomechanical function and patient reported outcomes of each subject while they are using three commercially available MPKs and a research grade powered knee, addressing the FY20 OPORP Focus Areas "Prosthetic Device Function" and "Prosthetic Device Form".

Hypothesis/Objective: Our *objective* is to personalize the prosthetic prescription process by creating a clinical decision algorithm for selection of an ideal MPK for an individual patient with transfemoral amputation (TFA) based on objective and patient reported data collected from that specific user. We test the *central hypothesis* that biomechanical and patient perceived differences will be detectable and predictable between different MPK components within a certain individual allowing for the creation of the first ever clinical decision algorithm for MPK component selection.

Specific Aims: Aim 1 will assess functional performance associated with use and wear of three different commercially available MPKs and one research grade powered knee in 17individuals with TFA. Aim 2 will assess subjective patient reported preferences associated with use of the same four prosthetic knees along with collection of subject specific anthropomorphic characteristics that may correlate with MPK choice. Aim 3 will generate the clinical decision algorithm for MPK selection.

Study Design: Our study revolves around clinical tests and outcomes measures to evaluate the biomechanical performance and patient reported outcomes of three different commercially available MPKs and a single research grade powered knee in individuals with a TFA. We will test the hypothesis that differences will emerge between individuals when wearing the different knees and that these differences will be predictable. Subjects will ambulate over various terrains to simulate community ambulation with each MPK (Aim 1) allowing for assessment of the functional performance of each MPK. Through collection of individual anthropomorphic data and psychometric outcomes measures (Aim 2), we predict individual preferences and biomechanical improvements will emerge between the various MPKs

allowing for the generation of a clinical decision algorithm for MPKs (Aim 3).

2. Participant population

Subjects will be individuals with above the knee and below the hip amputation. This vulnerable population group will be protected through the use of safety equipment such as hand rails and a safety harness for the case of stumbles and falls. The goal is to collect data from at least 17 participants.

Inclusion Criteria:

You may participate in this study if you meet the following criteria:
-A unilateral transfemoral amputation of the lower limb at least six months post fitting of definitive lower extremity prosthesis
-Habitual use of a lower extremity prosthesis in daily living activities (based on assessment of a physiatrist and/or prosthetist and patient self-report)
-Aged between 18 to 75 years
-K3 or K4 level ambulators who can perform all locomotor tasks of interest (based on assessment of a physiatrist and/or prosthetist)

Exclusion Criteria:

You will be excluded from participating if any of the following apply to you:
-Individuals with any significant neuromuscular or musculoskeletal disorder or other comorbidity that would interfere with participation (based on assessment of the physiatrist and/or prosthetist and patient self-report)
-Individuals who have open wounds on their residual limb
-Individuals with known visual impairments that would prevent them from safely operating a prosthesis during over ground walking or ascending stairs (based on assessment of the physiatrist and/or prosthetist and patient self-report)
-Individuals with known hearing impairments or who use hearing aids that would prevent them from responding to an auditory instruction (based on assessment of the physiatrist and/or prosthetist and patient self-report)
-Individuals who are currently pregnant (based on patient self-report) due to slight risk of falling during experiments

All participants that meet the appropriate criteria will be recruited through official flyers and verbal scripts, even if they are already known to the researchers. Flyers will be posted around the campus of Georgia Institute of Technology as well as the general Atlanta community and in partnering clinical facilities, in designated advertising areas. Additionally, word of mouth recruiting will use a script with similar language as the flyers. The study may also be advertised during various outreach events (in-person and/or virtual). Advertisements may be sent out via email lists, patient advocacy websites and online forums, and other online resources including but not limited to our own lab websites. We will also request that our clinical colleagues and collaborators provide interested patients with information about the study and refer them directly to us if their patients are interested in participating. Recruiting materials are attached as separate documents including a flyer and e-mail script. Permission will be obtained from participants before using any information for research purposes that has individual identifiers attached.

3. Study Procedures

Upon recruitment and informed consent, participants will proceed through the following protocol steps until they have been fit with all 4 prosthetic devices in total.

Randomization & Blinding: The order with which each subject will be fit with an MPK will be randomized using a random number generator prior to enrollment. Subjects will not be blinded to device type as appearance of each device is a variable that may influence patient reported outcomes. Blinding of study personnel is not possible given that component-specific knowledge is required to tune each of the different MPKs. Data will be blinded for data analysis procedures to reduce any potential bias.

Study procedures:

1. Each device will be measured for length (overall build height) and weight prior to use in the study. Weight of devices will not be controlled due to anticipated effects on the outcomes and thus the final best selection.
2. Anthropomorphic data will be collected from each subject to include cause of amputation, K-level, waist circumference, leg length, residual limb length, build height between distal residual limb and knee center, weight, height, BMI, gender and age. These variables are unique characteristics associated with an individual which may have an impact on their successful use with one device over another. This data will only need to be collected once from each individual participant.
3. Subjects will be administered the Patient Scales of Preference and Importance survey to understand how they individually rank priorities with regards to their prosthetic care and aspects of their daily life. The AMPnoPro will be administered to the subject while they are not wearing their prosthesis to attempt simulation of a patient with a new amputation that has gone through physical therapy and ready for a definitive prosthesis. AMPnoPro has been shown to be predictive of the functional level of an amputee. [1]

Subjects will then undergo fitting and alignment of the prosthetic knees in a randomized order.

4. Acclimation time varies widely in the literature (from 3-10 hours [2, 3] to months [4]) and is acknowledged to have important implications for this study's results. In this study, subjects will go through an initial tuning and training process similar to what is done in clinic scenarios including tuning knee parameters and training over the various terrains in the lab including stairs, ramps and a treadmill. Subjects will then proceed to wear the prosthesis for 1 week at home and in the community in order to acclimate to the device and then return to the lab for testing. A sensor to collect data about the number of steps participants take will be attached to the prosthesis and/or your shoes. This sensor does not have a GPS and will not record where subjects go. Subjects will use their same socket, prosthetic foot and shoe during each knee evaluation to ensure that differences observed during the study are attributable to the knee.
5. Subjects will ambulate five times over the 18' instrumented gait mat to determine their self-selected walking speed (SSWS) and GVI. Subjects will complete a 2-minute walk test and then be administered the Borg RPE.[5] A heart rate monitor will be worn during the 2 minute walk test in order to calculate physiological cost index (PCI) [6]
6. Subjects will proceed to walk up and down an overground 5-degree ramp for ten trials and then walk up/down a 6-step stair case for ten trials while we measure lower body 3D biomechanics and completion speed.

7. Subjects will walk across a beam while wearing the prosthesis. The beam is very low in height and sits only ~2" inches off the ground.
8. Subjects will walk on a treadmill while wearing the prosthesis while we measure lower body 3D biomechanics.
9. Subjects will then fill out the OPUS HRQOL, LEFS, PEQ, Veteran SF-36, and fall history survey to assess their perception of performance and other health related quality of life factors associated with use of each device. Pilot work with these surveys indicates this will take approximately 30-45 minutes.
10. Subjects will repeat Steps 4-8 with periods of rest provided as necessary until they have completed the full protocol for each of the three MPKs and research grade powered knee.

During all testing participants are instructed to vocalize any concerns or discomfort to researchers. Tests that occur in the lab will occur with the use of a safety harness and or gait belt. During tests, verbal feedback from the participants will be used to improve the comfort of the devices. Participants are instructed to notify researchers if they feel unsafe, and may quit the study at any time without penalty. Additionally, participants may be asked to wear EMG sensors, markers for measuring biomechanics and other mechanical sensors (such as IMUs) All participants will be guided through the following general procedure during their visits, requiring action on their part:

- Participants will be briefed about the details of and their rights during the study.
- The prosthesis and attachment interface will be fit to the participant, along with any additional data collectionequipment.
- Participants will be guided through the specific activities of the study, detailed already.
- Participants will receive assistance removing any sensors used during the study.

Other equipment may be utilized to measure biomechanics of the user during ambulation. Specifically, we will be using a VICON motion capture analysis system and an instrumented treadmill. This will also us to measure biomechanical similarities and differences while using the powered prosthesis compared to the sound side limb. Also, some protocols will require the use of an EMG (electromyography) system to measure muscle activity across different ambulation tasks. Three systems may be used which includes the Delsys Trigno Wireless EMG system, Biometrics Ltd. EMG system, and COAPT EMG system. All of these systems will use electromyography sensors that will be placed on the surface of the user's skin.

In order to also measure functional clinical measures, a Protokinetics gait mat will be utilized to measure common measures such as step length, step time, and symmetry. This system is just a mat that users will need to walk on top similar to walking overground. Users will be in a harness and have the options for handrails or gait belt if needed.

Throughout the tests there will be a camera recording the session. The purpose of the camera is to record performance for future analysis. The participant will always have the right to stop the test and/or take a break. The participant may also choose to discontinue participation at any time.

During the first visit, fitting and tuning will be no longer than 4 hours. Participants may end the visit at any time without penalty, or choose not to return for additional visits. If the participant agrees to continue the study subsequent visits will be scheduled at their convenience and pending availability of the prosthetic knee joints. During these subsequent visits, testing will last between 2-6 hours based on participant comfort.

Participants will be asked to attend at least 5 sessions in order to compare the effectiveness of the different prosthetic knees. However, each participant will maintain the right to discontinue their involvement for future sessions. Depending on the progress of the tests, participants may be involved in sessions ranging over the course of a few months.

The results of the study will be in the form of device performance and participant feedback. Sensor data will record the movement parameters of the subject. This includes mechanical instruments on the device and biomechanical instruments attached to both the device and the human subjects. These instruments will give information about the kinematics (movement), kinetics (force), muscle activity, step count, heart rate and metabolics of the user. This allows for the effectiveness of the design strategy to be assessed. The participants will also give feedback in the form of verbal conversation. This verbal feedback will deal with the comfort, convenience and preferences of the devices and controllers.

This study will use statistical analysis to compare between different intent recognition systems. We will use intent recognition accuracy as the primary metric to compare statistical differences across conditions. We will compare biomechanics between the powered device and a passive prosthesis. Typically, ANOVA tests are used with repeated measures to compare across multiple conditions.

Statistical & data analysis plan

A repeated measures ANOVA with within factor MPK will be used to assess differences across treatment for Aims 1 and 2, provided assumptions are met. In the event of missing data or violation, a linear mixed models procedure, which does not assume compound symmetry, will be considered. Bonferroni-Holmes correction will be made to control for family-wise error rate. Samples size calculations are outlined below. Estimated effect size was calculated using Cohen's d for within factor designs [71], assuming a correlation among repeated measures of 0.5. Effect sizes were then converted to Cohen's f for sample size estimations using G*Power. [72] **Aim 1: Comparison of clinical outcome measures on MPKs**. A Borg RPE of 2 (pooled SD= 2) was deemed clinically relevant for this study, resulting in an effect size of 1. Gait variability index effect size was based upon minimally detectable change (MDC) cited in [73]. An MDC of 8 and hypothesized pooled SD of 6, produced an effect size of 1.3. These data indicate a sample size of approximately 9 will achieve 90% power. The sample size proposed in this study (N=12) should ensure adequate power, even in the event of attrition or slightly higher variability. **Aim 2: Patient reported outcomes.** Resnik & Borgia (2011) have suggested a MDC of 10.3 (90% CI) for OPUS lower limb function.[61] Effect size for this study was calculated using MDC of 10 and a pooled SD of 7.7, assuming higher variability than previously reported SD's for upper

extremity [73]. This resulted in a Cohen's D of 1.3. Resnik & Borgia (2011) also reported PEQ subscale MDC's which ranged from 0.8-1.4 with Std errors of 0.3-0.6.[61] Based upon an MDC of 1.1 and SD of 1.25, Cohen's d would be 0.88. The sample size of 9 corresponds to 80% power. The SF36V will be used as an additional measure of health related QOL but due to high variability reported in the literature (from the inclusion of both mental and physical function scales)[61], this measure will not be powered by this preliminary study. Instead, this measure will be used to look for clinical trends in the data and aid in potential direction for the future larger study outlined in our transition plan. **Aim 3: Clinical Decision Algorithm**. The creation of the clinical decision algorithm for personalizing the MPK prescription to an individual is an exploratory, informative analysis that is constrained by population size and resources. Repeated sampling is employed to increase the information gained while attempting to minimize within subject variability and provide better examination of relationships. It is expected that in initial development, large effect sizes will be detected which play a critical role in the satisfaction with the use of prosthetic devices. To be valuable to clinical decision making, it is imperative that identification of this causal mechanism include factors other than solely clinical measurements. In addition, proximal outcomes, based on existing knowledge, will supplement the model. This process will lay the groundwork for the decision tree to be refined over time as the sample can be increased. There are a number of models that can be used for this aim (Bayesian approaches, linear discriminant analysis for repeated measures, etc.) which do not require as large a sample size for estimation procedures. The choice of model will be determined based on the underlying data structure by our co-I biostatistician, Dr. Teresa Snow.

4. Research Risks

The prosthetic knees have hydraulics and sensors. This type of device is classified as a prosthetic component and is a FDA Class I device. This means that it is a low-risk type of medical equipment. Although these procedures are very safe and commonly used in our lab, participation in this study may involve the following risks: The primary risk of injury in this protocol would be due to falls, regardless of the prosthesis being used. To minimize this risk, participants will be asked to wear a safety harness and initially walk with handrails until they become comfortable using the prosthetic device(s) and demonstrate that they can use it without falling. Should participants fall during this familiarization session, the harness will support them. When walking overground, participants will still have the option of wearing the safety harness, access to hand rails or other walking aids, and may be supported by staff members using a gait belt as you complete the activities. When participants wear the prosthesis at home, they will not have access to a harness or gait belt. This is similar to what happens in clinical scenarios when a prosthetist fits a patient with a prosthetic component; while in the clinic, familiarization occurs and then the patient is sent home to use the device independently.

A second risk is muscle soreness and fatigue. Muscle soreness is a common

problem when walking with a new prosthesis. To prevent this, experimental sessions will be kept as short as possible, adequate rest periods will be provided between trials, and participants will be questioned often about any discomfort.

A third risk is skin irritation. Skin can become irritated while using any prosthesis and it may also become irritated by adhesive reflective markers. Additionally, the residual limb will be checked prior to and after the study to inspect for skin irritation or if participants experience discomfort in their residual limb during the study, we will give time for the socket to be removed to allow for appropriate inspection. To avoid the risk of skin irritation, participants will use your normal, take-home socket.

A fourth risk is that participants may find that they prefer a different prosthetic knee following use of the various knees within the study and may not be able to obtain this knee through your clinical provider and/or insurer. We will provide all information to you that you request regarding your performance in the various knees but the goal of the study is not to provide participants with a knee to take home following the study.

5. Confidentiality

Participants will sign a consent form before participating which explains that no identifiers linking them to this study will be included in any sort of report that might be published except for the video taken. Participant faces will be blocked out upon request. They will be given a pseudonym different from their own name that will be referred to in studies published, if at all. Participants will be assured in the informed consent that the data will be used only for studies that are consistent with the original research purpose.

This consent form will be filed securely in an official area. People who have access to information include the Principal Investigators and research study personnel. Representatives of regulatory agencies such as the Office of Human Research Protections (OHRP), the Food and Drug Administration, the DoD, and entities such as the Georgia Tech Office of Research Integrity Assurance may access participant records to make sure the study is being run correctly and that information is collected properly.

Information about participants related to this study will be kept confidential to the extent permitted or required by law.

When the data is stored, it will no longer be linked to the subject's personal information. There will be a master list stored separately that connects the subject identifiers with their personal information, for when they need to be contacted. The data will be kept on the computers of the research personnel only. These computers will all be password protected to prevent non-authorized access to the data. Data will be transmitted electronically between researchers. The master list of subjects and their personal information will not be transmitted in any form between researchers. This master list will only be in the possession of the PI and researcher responsible for recruiting. It will not be shared with anyone else in any way.

6. Benefits

Our goal is to optimize the prosthetic prescription process for currently available

MPK devices as there is no current understanding for which MPKs are best suited for which patients. The long-term goal of this research is to improve the ability of people with amputations to be able to walk better and more easily: including walking on level surfaces, stairs, ramps, hills and other activities.

7. Compensation

Subjects will be paid at $20/hour while they are in the lab and an addition $300 once they complete the full study to incentivize all subjects to complete the full study which is important for our results. Free parking will be provided to all subjects when they come to campus for experimental sessions.

Subjects will be given the choice of compensation via check which will be issued through USPS mail to their home (or a provided) mailing address or a gift card which will provided at the end of each visit to the lab.

8. Costs

There are no direct costs to study participants. The costs to participants for this study will most likely be only their time and energy. Participants will be responsible for covering any unforeseen costs including, but not limited to, transportation to the research location, parking expenses, food, or child care.

9. Alternatives

Participants are informed that participation in this study is voluntary. It is made clear that they have the right to change their mind and leave the study at any time without giving any reason and without penalty. Any new information that may make participants change their minds about being in this study will be given to them.

10. Consent/Assent Process and Documentation of Consent/Assent

After being informed about the study through recruitment by way of flyers, e-mail or word of mouth, participants will be given a consent form outlining details about the study. The consent form provides detailed information about the study procedures. When reading through the consent form potential participants are encouraged to vocalize any questions they have including, but not limited to, inquiries about testing procedure, risks of the study and participant rights. Questions will be answered by the researcher personnel conducting the study. Participants will be given as much time as they need to make a decision about whether or not to participate. During this process, as well as throughout testing it will be made clear that participants may chooses to end the study at any time, no questions asked, and will not face any negative repercussions. Signing of the consent form will take place in person where researchers present will answer any questions then obtain their signatures. This consent form will be filed securely in an official area, that can only be accessed by Principal Investigators of this study and research study personnel. Participants will be given a copy of this consent form and do not waive any legal rights by signing it.

The only personal information we will collect is the participant's name, telephone, email, and contact information. This information will not be published in the research results, nor will it be used to perform data analysis. This information will also not influence the

results of the research. We only collect this information so we can contact the participants and refer to them by their names during conversation.

11. Investigator's Qualifications

The PI, Dr. Aaron Young, has conducted a number of experiments similar to this one with amputees. The Co-PI, Kinsey Herrin, is a certified prosthetist specifically trained to work with individuals with amputation and fit prosthetic devices to them. Three of the prosthetic knees used in this protocol are clinically available through manufacturers and used broadly in the prosthetics clinical community. These are the devices that will be brought home for 1 week testing protocols with participants. The fourth device is our own experimental investigational device and the testing of this device was IRB approved previously at Georgia Tech with a separate, but related protocol. All members listed on this IRB protocol have CITI training.

12. Funding Sources

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