RESEARCH PROTOCOL

Evaluating Mobility Interventions in the Real World

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Project Summary

This project is intended to test the comparative biomechanical benefits of different lower-limb prostheses and orthoses using data collected over extended periods of everyday life using wearable sensors. We seek to improve physical health, functional activity level, independence, workforce participation, and mental health in persons with lower limb amputation and other lower-limb impairments. We seek to study the similarities and differences in their movement using prostheses and orthoses with different technological features or designs. We also seek to develop technologies that enhance the methods for using wearable sensor technology to perform this type of study.

Subjects with lower-limb amputation, subjects who use lower limb orthoses, subjects with drop-foot (including a specific group with Multiple Sclerosis), and healthy control subjects will be recruited in this study. Subjects of all groups will be tested for biomechanical performance and optionally for caloric energy expenditure during balance and locomotion tasks including standing, walking, running, ascending and descending stairs and ramps, walking on sloped terrain, and walking on uneven terrain. Subjects with amputation will use a variety of commercially available prostheses to test the effects of certain prosthesis properties or behaviors. The effects of different conditions will be assessed using both repeated-measures experiments in a laboratory and long-term repeated-measures observational studies using data from wearable sensors. Subjects who use lower-limb orthoses or who have drop-foot will perform similar tests using multiple types of orthotic interventions including ankle braces and functional electrical stimulation devices. Subjects with intact limbs will perform tasks while wearing ordinary shoes to provide normative data. They may also perform tasks while wearing a prosthesis simulator (walking casts or leg braces that lock or circumvent the ankle, to which prosthetic feet can be attached) and lift shoes, in order to test the function and durability of the prostheses. Finally, they may perform tasks while wearing lower limb orthoses. Measurements may include body segment motion (from optical motion capture and/or wearable inertial sensors), ground reaction forces (force plates), loads in the tibial pylon of the prosthesis (pylon load cell), foot sole pressure (pressure-sensitive insoles), electromyographic signals (EMG, using skin electrodes), energy expenditure (respiratory gas exchange), ambulatory device usage (by inertial measurement sensor), outdoor location (GPS), indoor location (based on wireless network signals and special beacons) and other measurements of movement and biomechanics. Outcomes may include spatiotemporal gait characteristics (e.g. walking speed, step length, step width, step time); motion of the body; characteristics of the paths a person traverses in everyday life; kinetic performance of joints and segments (force, moment, impulse, power, work); and other biomechanical performance measures.

Relationship between UW and WRNMMC: The overall project has components at two locations – the University of Wisconsin – Madison and Walter Reed National Military Medical Center (WRNMMC) – but it is **not** being treated as a multi-site study. The protocol presented here covers experiments at UW-Madison as well as transfer of data from WRNMMC and analysis of data from both sites, but it does not cover activities specific to the experiments at WRNMMC. This section explains the reasoning for this approach, for the sake of clarity in review.

The WRNMMC site and the UW-Madison site are being treated as separate studies for purposes of IRB approval. The reasons for this are several. First and foremost, the DOD Human Research Protection Office (HRPO) recommends the use of separate approval for each site in DOD-sponsored research. HRPO is required to approve the protocols at each site of any research sponsored by DOD, and a multi-site study must continually maintain compatible protocols across all sites through this additional layer of oversight and administration. Because local IRB requirements can differ, HRPO recommends treating the sites as separate so the pain of resolving differences can be avoided. Second, the activities at the two locations (UW and WRNMMC) are not intended to be identical. UW-Madison is responsible for developing wearable sensors, pilot testing the technology, and developing algorithms to process it, whereas WRNMMC is a data-collection site only. Third, UW-Madison and WRNMMC are also testing different things: UW will perform pilot tests with different prostheses and orthoses as part of the methods development, for shorter time periods (1 week) and with less biomechanical testing. WRNMMC will test specific properties of the prostheses using longer periods (3 weeks) and more extensive in-lab biomechanical testing. Because the protocols differ, they will produce separate data pools. There is the possibility that some portions of the data pools can be combined to yield broader results, but this is different from conducting a true multi-site study. Therefore, we believe the strategy of treating each site separately with its own IRB approval is both convenient and correct for this study.

UW-Madison will be the primary data processing site for all portions of the study, so this protocol contains information on how data will be transferred between WRNMMC an UW-Madison. These procedures include coding of data at WRNMMC, and retention of the code key only at WRNMMC so that UW will not have access to direct identifiers. Similarly, any data generated at UW and shared with WRNMMC will be coded and the code key will be retained at UW only. UW is also the primary site and home of the project PI, so this protocol includes information about on-site interaction among staff from the two sites. The purpose of such interaction is to allow UW personnel from UW to travel to WRNMMC to provide training on the use of the sensor systems, observation of the experiments on-site at WRNMMC, and demonstration of the processing and data interpretation algorithms developed at UW. Staff from WRNMMC may also come to UW for training, observation and demonstration.

Part I: Overview of Potential Procedures and Outcomes

Background and Significance

Prostheses:

Transtibial and transfemoral amputees require the use of ankle-foot and knee-ankle-foot prostheses for bipedal ambulation. Prosthesis performance is a critical factor in the health and well-being of persons with lower-limb amputation. However, traditional passive prostheses, even modern Energy Storage and Return (ESR) prostheses and multi-axial (MA) prostheses, are inadequate for producing biomimetic gait patterns across locomotor functions required for activities of daily living [1]. To better mimic the human lower limb, advanced prostheses have been developed that achieve greater adaptability to the different tasks and terrains a person encounters. These features include passively adapting properties such as user-adjustable hydraulic damping in the ankle or knee, or actively adapting properties such as computer-controlled hydraulic damping or robotic control. The addition of these features is expected to improve walking and other movements, and some evidence in the laboratory indicates preference, improved biomechanics, and higher walking speed [2]–[9] in comparison to the shortcomings of existing passive prostheses [10]–[13]. However, the effects of these prostheses on everyday life have been difficult to measure. One recent study found strong preferences for prostheses with greater compliance than others, but no difference in activity as tracked using a step counter [14]. This discrepancy leaves a gap in clinical evidence to support prescription of the different designs for different persons.

Therefore, we plan to test a variety of passive and semi-active lower-limb prostheses that are currently available in the marketplace, using more advanced wearable sensors to compare how different devices and features affect movement inside and outside the laboratory. We plan to compare movement with standard-of-care Energy Storage and Return (ESR) prostheses against movement with more advanced Passive Hydraulic Ankle (PHA) and MicroProcessor-controlled Ankle (MPA) prostheses. We will evaluate outcomes associated with biomechanical variables such as limb loading and foot movement, including load on the prosthetic socket, stride length, toe clearance, and others.

Orthoses:

Like prostheses, lower-limb orthoses have long been a common means of improving mobility for persons with a variety of impairments. One of the most common impairments is drop-foot (also called foot drop), which arises from a range of neural injuries including central and peripheral insults, neuropathy, and trauma. Orthotic solutions to treat drop-foot include rigid or elastic ankle-foot orthoses (AFOs) and functional electrical stimulation (FES) neuro-orthoses. But, as with prostheses, there is currently a lack of evidence to support prescription of one intervention over another in clinical practice.

Therefore, we plan to test different orthotic treatments for lower-limb impairment, to

determine how different devices and features affect movement inside and outside the laboratory. We plan to test standard plastic or carbon-fiber AFOs against the alternative treatment, an FES stimulator that stimulates the ankle dorsiflexors, for their effects on real-world movement in persons with drop foot. We will evaluate similar outcomes including toe clearance and gait kinematics using both devices.

Real-World Movement Assessment:

As mentioned above, most information about how prostheses and orthoses affect individuals in their daily lives is inadequate for guiding truly evidence-based care. Current research assessing outcomes and developing standards of care is based on either (i) focused, laboratory-based studies, or (ii) low-resolution estimates of activity level outside the laboratory, such as step counts and self-reported user experience [14]–[17]. Both approaches have drawbacks that make them inadequate for accurately assessing the effects of interventions on outcomes. Laboratory tests measure only a few movements, at a very specific point in time, often before individuals develop stable adaptations to new devices or conditions. Step count approaches have minimal information (only step count in e.g. 1-minute intervals), can be heavily influenced by external factors like work or social responsibilities unrelated to any interventions, and are shown to be insensitive to changes in prosthetic device properties. Self-reported longitudinal experience is notoriously inaccurate and subject to bias.

Therefore, we are developing methods for using a person's own behavior in daily life as a replacement for controlled laboratory research protocols. We will apply these new methods to evaluate the differences in behavior among specific biomechanical devices such as prostheses, orthoses, or types of footwear. The potential benefits of this approach include eliminating the need for laboratory protocols in some instances, and improving the ecological validity of data used to determine the benefits of different treatments, due to recording during unsupervised real-world movements.

The scientific approach is to evaluate the statistical differences among aggregated samples of movements on frequently repeated paths in everyday life, under different experimental conditions (such as different prostheses, orthoses or shoes). We will track a person's movements outside and inside buildings using wearable inertial sensors, environmental sensors (e.g., barometric pressure, temperature, humidity), and location sensors (e.g., GPS, computer network signals, dedicated beacons). We will identify specific paths (sidewalks, hallways, stairways, corners, etc.) that are frequented by an individual. We will identify each bout of movement along these paths and build sets of "comparable bouts" on the same path across multiple days and experimental conditions. We will repeat this procedure for multiple different devices and compare the effects of these devices on habitual movement.

Project Goals:

The immediate goals of this project are (i) to compare the effects of different types of features

in lower limb prostheses and orthotic solutions; and (ii) to develop methods for analyzing the effects of mobility devices on locomotion in real-world environments.

Aims

Aim 1:

To develop methods for using wearable sensors and long-term monitoring to assess changes in gait due to different mobility interventions, and to study the effects of different interventions using these techniques.

Aim 2:

To compare the effects of different features of prosthetic feet on movement quality in everyday life.

Aim 3:

To compare the effects of different orthotic treatments on movement quality in everyday life.

Study Objectives

Primary objective

To determine the comparative biomechanical benefits of prosthetic foot-ankle systems with different features to persons with lower-limb amputation.

Secondary objectives

To determine the comparative biomechanical benefits of different orthotic solutions to persons with drop-foot.

Tertiary objective

To perfect methods for collecting and analyzing data from wearable sensors to compare the benefits of different conditions on everyday movement.

Study Outcomes

Primary outcome

The primary outcome is biomechanical gait function, as measured through gait metrics such as limb and joint movement patterns and foot placement variability (kinematics), and joint and prosthetic socket loads and joint power production (kinetics).

Secondary outcome

The secondary outcome is behavioral gait function, as measured from preferred walking speed, stride count, breadth and perceived ease of locomotor activities, and reports of inconvenience, pain and discomfort.

Research Design and Methods

In this protocol we will perform short-term laboratory and long-term real-world locomotion testing with a variety of commercially available lower limb prostheses and commercially available orthotic solutions for drop-foot, with emphasis on using wearable sensors to compare biomechanical performance with different devices.

Subjects will perform testing inside the laboratory ("lab testing"), outside the laboratory ("field testing") on and near the campus of UW-Madison, and/or extended testing in a home and community environment ("take-home testing") to evaluate different aspects of device function. Lab testing may consist of standing (on one or both legs), walking (at various speeds, forward and backward), and running (from running in place to a fast jog) trials, performed on a standard treadmill, an instrumented split-belt treadmill, a moving treadmill with virtual-reality surround screen, on ramps, on stairs, and/or on the floor. Measurements will be made using standard biomechanical measurement tools such as motion capture, wearable motion sensors, force transducers, pressure insoles, electromyographic electrodes, treadmills, and respiratory gas sampling equipment. Field testing may include standing and walking trials, conducted indoors and outdoors, on level ground, uneven ground, slopes, and stairs, as well as level running. Take-home testing will consist of wearing one or more different prostheses, orthoses, or types of footwear, together with wearable sensors to evaluate their function, for periods ranging from hours to weeks of everyday life.

Figure 1: Examples of prostheses that may be compared in the experiment: energy storage-and-return prostheses (ESR, left); ESR with passive hydraulic ankle (PHA); and ESR with microprocessor-controlled ankle (MPA). Examples shown are Endolite Esprit, Echelon, and Élan. Specific prostheses from multiple manufacturers will be chosen in the course of the research.

Experiments will use standard commercially available prostheses for persons with lower-limb amputation. Specific prostheses will be determined at the time of the study, but they will include prostheses that are fully passive such as energy storage-and-return (ESR) feet, ESR feet with mobilized ankles such as passive hydraulic ankles (PHA), and ESR feet with microprocessor-

controlled ankles (MPA). Examples from one manufacturer (Endolite) are shown in **Figure 1**. A separate branch of the study will use multiple presecribed prostheses that an individual already possesses – specifically a daily-use prosthesis, a running-specific prosthesis, and any other prostheses (including but not limited to activity-specific prostheses). For orthosis users, standard commercially-available orthoses or standard-of-care custom orthoses will be used, as well as a standard commercially-available electrical stimulation neuro-orthoses (BioNess –**Figure 2**). For persons without impairment, different footwear will be used. Each person will use two or more different prostheses or orthoses in the lab and in periods of one to three weeks of everyday life.

We will perform laboratory testing at the beginning and end of the period using each device, except in the cases of individuals using their own devices whose schedules or locations necessitate off-site installation (no lab testing for these individuals – they will complete the take-home portion of the study only). For each device, we will perform standard gait and movement analysis. During field testing and take-home testing, participants' locations and motions will be recorded with a combination of global positioning system (GPS), wearable inertial measurement unit (IMU), Bluetooth and Wifi network sensors. During take-home testing, data will be recorded continuously during all waking hours when the participant uses the sensors. Unimpaired subjects may also be invited to participate in the take-home study to provide normative data with different types of footwear. Take-home portions of the study will last at most 10 weeks. Subjects in the off-site installation group will only perform everyday-use testing, in which wearable sensors on their existing prostheses (and potentially cell-phone GPS) log data while they use each of their prostheses.

Figure 2: Orthotic drop-foot aids for potential use in the experiment: an ankle-foot orthosis (left), BioNess FES Neuroorthosis (right). The Bioness FES device senses leg motion and stimulates the peroneal nerve during swing

phases of gait, causing the dorsiflexor muscles to lift the foot for improved ground clearance.

Biomechanically intact persons will perform normal locomotion activities such as standing, walking and running, while standard and novel biomechanical measurements are taken. The activities may include some or all of the following:

- Standing still, with eyes open or closed, on flat or sloped surfaces that are stiff (normal) or soft. These standing activities may be performed on standard force plates or on a force plate that estimates stability from characteristics of the ground reaction force signals under the feet and moves the surface and a visual surround to perturb balance.
- Walking at a range of speeds, forward or backward, on flat, uphill, downhill, or side-hill surfaces, or stairs. Surfaces may include indoor and outdoor ground, and/or an instrumented treadmill that measures ground reaction forces under both feet.
- Running in all the same conditions as walking.
- Performing any of these activities barefoot or with various shoes or boots.
- Performing any of these activities using "prosthesis simulators" on one or both legs. Prosthesis simulators are designed to allow an intact person to use a foot-ankle prosthesis by holding the natural foot out of the way.
- Performing any of these activities spontaneously while wearing long-term monitoring sensors in everyday life.

Persons with lower-limb amputation will perform all the same tests described above in biomechanically intact individuals, but using a variety of commercially-available lower-limb prostheses. The prostheses may be of many kinds exhibiting different behaviors and properties, including but not limited to:

- Standard wood, plastic and foam prostheses.
- Carbon fiber or fiberglass prostheses with high energy storage and return.
- Prostheses with passive or manually-adjusted mechanisms to alter properties such as stiffness or damping.
- Prostheses with microprocessors that control their motion or properties such as stiffness, damping or joint angle through active adjustment.
- Running-specific and other activity-specific prostheses.

Running tests will be limited to those who are already habitual runners.

Persons with drop-foot will perform all the same tests as those with lower-limb amputation, using different orthotic solutions. The orthotic solutions may include braces of various kinds as

well as neuro-orthoses, including but not limited to:

- Standard orthoses, made of plastic, fiberglass or carbon fiber, with or without hinges.
- Custom orthoses with special structural features such as custom stiffness, novel support surfaces, or energy return properties.
- Functional electrical stimulation (FES) devices that stimulate the peroneal nerve to activate the ankle dorsiflexor muscles.

Orthoses may be designed and built by orthotists associated with the study team according to standard clinical practices, or they may be purchased off-the-shelf according to standard clinical prescription practices. Running tests will be limited to those who are already habitual runners.

The subgroup of persons with Multiple-Sclerosis and drop-foot will perform all procedures as described for persons with drop-foot, but enrollment will be restricted to MS patients.

All participants may be subjected to a variety of measurements:

- Weight and size measurements for scaling biomechanical models.
- Use of skin-mounted reflective markers for motion capture in a research-grade motion laboratory.
- Measurements of strength such as manual muscle testing with or without dynamometry.
- Measures of gait and balance function
- Force measurements under the feet using in-ground force plates, balance plates, load cells installed in a treadmill, or pressure-sensitive shoe insoles.
- Measurements of muscle activity through skin electrodes.
- For persons with amputation, force measurements from a load cell installed in the prosthetic pylon.
- Miniature inertial sensors (accelerometer/gyroscope/magnetometer) systems mounted on the feet and other body segments.
- Environmental sensors (temperature, barometric pressure, relative humidity, etc.) mounted on the leg
- Tracking of assistive device usage via inertial measurement sensors attached to the subject's ambulatory assistive device(s)
- Location tracking through a global positioning system (GPS) receiver or cell phone app, either carried or worn on the body
- Supplementary indoor tracking system, such as a Bluetooth beacon (to be placed in a frequented location by the participant), or a Wi-Fi signal-based tracking app on a cell phone or other body-worn computer

- Measurement of respiratory gas exchange (oxygen consumption, carbon dioxide production) during movement to estimate energy expenditure.
- Voice recordings to capture key comments subjects make about the devices or to record events that occur during daily life.
    - The voice recordings are necessary as an alternative to written records so that for any event a firm time stamp can be established, enabling analysis of the event according to the time-stamped movement records. Written records are also known to be unreliable.
    - Recordings are limited to notable events related to this mobility study, such as: any trips, slips, falls, or losses of balance; locomotion on unusual terrain; activities of special note such as running or participation in sports; and any malfunction of the other sensors.
- Photographs and videos for analysis and presentation
    - Non-identifiable images will be recorded as a record of the experiment.
    - Identifiable images will be recorded only with specific consent for identifiable images.

Subject identification and Recruitment

Target Population and Enrollment

The target enrollment is 20 persons with transtibial amputation and 10 persons with drop-foot at UW-Madison, and up to 20 healthy controls to test the methods. Additional participants with transfemoral amputation (up to 10) may also be enrolled at UW-Madison. Additional participants with transtibial and transfemoral amputation will be recruited at the remote site for a separate data pool (Walter Reed National Military Medical Center, WRNMMC). All subjects will be 18-75 years old, representing the main target population for whom these devices could improve daily life.

We will recruit subjects following inclusion and exclusion criteria mentioned below.

Target Populations:

- The first target population is persons with lower-limb amputation who use prostheses for ambulation.
- The second target population is persons with drop-foot.
    - A targeted subset of the drop-foot population will be persons with Multiple Sclerosis and currently drop-foot.

Inclusion:

Target Populations:

- Subjects will be age 18-75 years at time of enrollment.
- Subjects with amputation must have used a prosthesis for more than 6 months, and wear it for at least 8 hours per day.
- Subjects must be more than 6 months past their most recent surgery (if any).
- Subjects must be free of musculoskeletal and cardiovascular conditions that would limit their ability to safely complete testing.
- Subjects should consider themselves in good health; be able to wear their prostheses or orthoses all day long; be able to perform all of their activities of daily living (ADL) with their prostheses or orthoses as appropriate, have a comfortably fitting functional prosthesis (if applicable) that does not cause any skin problems; and have a stable residual limb (or impaired limb).
- Subjects may use a narrow-base cane (single point, narrow tripod base, etc.) as an ambulatory aid but not a small-base quad cane, wide-base quad cane or walker.
- Subjects must be able to walk with their prostheses or orthoses for 30 minutes (total) and stand for 30 minutes (total), in individual bouts of at least 7 minutes, without becoming fatigued, feeling dizzy, having chest pain or shortness of breath, or experiencing claudication symptoms.
- Subjects most report an estimated average daily walking time of at least 45 minutes outside of the home. This does not need to be continuous and considers walking for all purposes.
- Subjects involved in running tests must be able to run for 30 minutes (total) in bouts of at least 6 minutes, without becoming fatigued, feeling dizzy, having chest pain, or experiencing claudication symptoms.
- Subjects must have no known cognitive disability.
- Subjects must be fluent in spoken and written English.
- Running portions of the study will be limited to subjects who self-report regular engagement in recreational or competitive running.
- Subjects in the branch that uses only their own prostheses must have at least a daily use prosthesis and a running-specific prosthesis; additional prostheses may also be included.

Control Subjects:

- Ages 18-75 years
- Subjects should consider themselves in good health, and be able to perform typical activities of daily living (ADL).
- Subjects may use a narrow-base cane (single point, narrow tripod base, etc.) as an ambulatory aid but not a small-base quad cane, wide-base quad cane or walker.
- Subjects must be able to walk for 30 minutes (total) and stand for 30 minutes (total), in

individual bouts of at least 6 minutes, without becoming fatigued, feeling dizzy, having chest pain or shortness of breath, or experiencing claudication symptoms.

- Subjects involved in running tests must be able to run for 30 minutes (total) in bouts of at least 6 minutes, without becoming fatigued, feeling dizzy, having chest pain, or experiencing claudication symptoms.
- Subjects must have no known cognitive disability.
- Subjects must be fluent in spoken and written English.

Multiple Sclerosis group:

- For the specific subgroup targeting Multiple Sclerosis, subjects must have a clinical diagnosis of Multiple Sclerosis and a clinician must determine they are experiencing foot drop.
- Subjects must be able to comfortably wear and ambulate with both study devices with effective management of foot-drop, without significant discomfort
- Subjects must be able to perform all of their activities of daily living (ADL) with only minimal use of ambulatory aids. Subjects may use a narrow-base cane (single point, narrow tripod base, etc.) as an ambulatory aid in any amount. Use of more comprehensive ambulatory aids (e.g. a small-base quad cane, wide-base quad cane or walker) must be limited to no more than 20% of their walking time when not at home. Individuals who do use an assistive device occasionally should report a threshold for use of greater than 100 feet, i.e., they are unlikely to use their device unless they anticipate ambulating greater than this distance.

Exclusion criteria:

Target Populations:

- Allergy to electrode gel, surgical tape and metals.
- Subjects who currently use the Bioness L300 Go or similar neuro-orthoses or use a carbon fiber ankle-foot orthosis for more than occasional use at the time of the study will be excluded to avoid biasing results for one device or the other. Occasional use for the purpose of this study is defined as more than 20% of walking time when not at home. Subjects with past experience who are not currently using these devices will be eligible.
- Subjects enrolled in physical therapy or other rehabilitative care for treatment of gait, balance, or lower extremity strength or coordination at the time of the study will be excluded to avoid confounding effects from therapy and device-based management of their condition.
- For the orthotics study, subjects with peripheral neuropathy impacting control of the tibialis anterior muscle via the peroneal nerve will be excluded.

- Subjects under treatment for infectious diseases will be excluded from the study.
- Women who are pregnant or planning to become pregnant during the course of the study will be excluded.
- Symptomatic musculoskeletal conditions that prevent unaided walking, such as back pain or knee arthritis.
- Cardiovascular conditions that make moderate exercise unsafe, including (but not limited to) history of angina, peripheral vascular disease, congestive heart failure, history of myocardial infarction, and history of stroke. Potential participants will be excluded if they self-report that a physician has told them to avoid moderate exercise.
- History of chest pain, shortness of breath, or claudication symptoms during ambulation
- History of significant neuropathy with altered balance
- History of serious residual limb pain or phantom limb pain within the past six months.
- History of chronic skin breakdown.
- Inability to perform the tasks involved in the study.
- Age under 18 or over 75 years at time of enrollment.

Control Subjects:

- Allergy to electrode gel, surgical tape and metals.
- Subjects under treatment for infectious diseases will be excluded from the study.
- Women who are pregnant or planning to become pregnant during the course of the study will be excluded.
- Symptomatic musculoskeletal conditions that prevent unaided walking, such as back pain or knee arthritis.
- Cardiovascular conditions that make moderate exercise unsafe, including (but not limited to) angina, peripheral vascular disease, congestive heart failure, history of myocardial infarction, and history of stroke. Potential participants will be excluded if they self-report that a physician has told them to avoid moderate exercise.
- Inability to perform the tasks involved in the study.
- Age under 18 or over 75 years at time of enrollment.

Persons in status relationships with members of the study team may be included in any of the groups. Recruitment of those with a status relationship may occur through indirect methods (posted flyers/ads and mass emails), or when these individuals learn about the study in the course of their participation in lab activities and/or interaction with members of the lab and study team. If these persons wish to enroll, the process will be handled by a study team member who does not have a position of influence over them. If the initial discussion involves the PI, the PI will state that he does not intend any pressure to participate, that the decision to participate is each

individual's alone, that there will be no negative consequences for non-participation, and/or similar statements, and will refer the prospective participant to another member of the study team for the rest of the recruitment, enrollment, and consent process. The Informed Consent process will be performed by a member of the study team who is not in a position of influence over the potential subject.

HIPAA compliant (REDCAP) email and/or text-messaging, depending on subject preference, will be used for efficient and consistent communication with participants. Participants will receive contacts from the study team with reminders regarding completing the patient-reported outcomes and upcoming study visits.

Subject Identification:

- Clinicians (rehabilitation physicians, physical therapists, orthotists and prosthetists) involved in the care of patients may identify potentially eligible patients as they come to clinics for routine visits.
- Many potential participants for this research are well-known to their clinicians, and communicate with them regularly outside of regular visits. Clinicians may identify these subjects from memory.
- Recruitment flyers may be posted at different locations such as the UWHC; the School of Medicine; UW Orthotics and Prosthetics clinic; UW libraries; the University Station Clinic; St. Mary's hospital; Meriter hospital; Madison public libraries; prosthetics and orthotics clinics in the Madison, WI area and other areas of southern Wisconsin and northern Illinois; amputee or mobility impairment support group locations, and on the web page of the UW BADGER Lab (http://uwbadgerlab.engr.wisc.edu).
- Recruitment emails may be sent to support group lists to advertise the study to their members (for subject self-identification). Emails to support groups will be sent no more than once per three months, always with the permission of the group mailing list moderators [email text provided in IRB application].
- A posting will be listed on the MS Society website for clinical trials: https://www.nationalmssociety.org/Research

Subject Recruitment:

- Clinicians throughout the United States (rehabilitation physicians, physical therapists, orthotists and prosthetists) involved in the care of patients may hand recruitment flyers to eligible patients and discuss the study with them [recruitment flyer attached to IRB application].
- Many potential participants for this research are well-known to their clinicians, and communicate with them regularly outside of regular visits. Clinicians may tell these

potential participants about the study by voice during these routine phone calls, or include basic study information in email communications they would normally undertake, or make a dedicated phone call or send a dedicated email message with basic study information. [email template attached to IRB application]. Alternatively, clinicians may send a physical letter to potential participants' mailing addresses. [Template letter attached to IRB protocol - "Individual Participant Recruitment Letter Template"]Recruitment flyers may be posted at different locations such as the UWHC; the School of Medicine; UW Orthotics and Prosthetics clinic; UW libraries; the University Station Clinic; St. Mary's hospital; Meriter hospital; Madison public libraries; prosthetics and orthotics clinics in the Madison, WI area and other areas of southern Wisconsin and northern Illinois; amputee or mobility impairment support group locations, and on the web page of the UW BADGER Lab (http://uwbadgerlab.engr.wisc.edu).

- Potential participants contacted by clinicians using these first two methods may be asked by the clinician to give permission to share their contact information with other members of the study team. If they give permission, the clinician will pass on their name, phone and/or email to one of the other approved members of the study team, who will reach out directly to the potential participant.
- Recruitment emails may be sent to support group lists to advertise the study to their members (for subjects to volunteer), with the permission of the group mailing list moderators [email text provided in IRB application]. Emails to support groups will be sent no more than once per three months, always with the permission of the group mailing list moderators [email text provided in IRB application].
- With permission of support group leaders, members of the study team may visit local support group meetings either virtually or in-person to present basic information on this study which is included in current recruitment materials, address any questions from persons in the group, and recruit participants.
- Volunteers (with or without prostheses/orthoses) may be recruited through flyers posted across the UW campus and downtown Madison. Flyers will only be posted where approved by the appropriate authority. [Sample flyer is attached]
- Volunteers (with or without prostheses/orthoses) may be recruited through an email blast to the UW community, through the Division of Information Technology (DoIT). [Sample text of the email is attached.] Emails through DoIT will be sent no more than once per year.
- Volunteers (with or without prostheses/orthoses) may be recruited through word-of-mouth. Study team members approved to perform recruitment may mention the study and/or hand out recruitment flyers to friends, family, neighbors, classmates, and others.

Participants responding to the recruitment flyer will be contacting a member of the study team

approved to perform subject recruitment, enrollment and consent. This study team member will describe the study briefly to each potential participant who responds to these recruitment methods. The subject will be screened and recruited during the first phone call or meeting, or at a later time. Recruitment and screening will be performed according to a screening script [attached] by members of the study team approved for these activities. Screening materials for persons who do not enroll in the study will be destroyed, unless the person gives permission to be contacted for future studies. If the respondent expresses willingness to participate in the study or to be contacted for future studies, his/her name, contact information, and potential group (prosthesis user, orthosis user, control) will be added to a list of interested potential participants. This list is for limited use by the study team for prosthetics and orthotics-related studies only.

During the telephone screening, the following information will be collected directly into ICTR REDCap as appropriate: name, preferred name, address, home phone number, mobile phone number, email address, age, birthdate, gender, height, weight, past medical history, past surgical history, and the answers to the telephone screening questionnaire. Electronic files will be removed from ICTR REDCap ten years following study completion.

Consent or Assent:

Alteration of Informed Consent:

We will request a waiver of written documentation for consent so that we may obtain oral consent for:

1. Retaining the notes taken during the telephone screening for eligibility and recruitment for future studies
2. Communicating via email and text messaging for study-related purposes

During a telephone screening for potential participants, we will obtain oral consent to retain the notes taken during the screening for up to 10 years for the purpose of inviting them to participate in future studies, and to communicate with them via email and/or text messaging for study-related purposes, which includes sending emails and/or texts that contain links to ICTR REDCap that will allow them to complete study-related questionnaires throughout the duration of the study as well as remind subjects of upcoming appointments.

Justification of Altered Consent: This study involves completing a telephone screening, questionnaires, and participating in clinical assessments and interventions that are common and currently in use in clinical practice at UW Health. These activities are similar to and of no greater risk than activities of daily living or that would be encountered during a standard clinic examination. The altered consent increases the feasibility of conducting this project (and future projects) by simplifying recruitment. These procedures also reduce the time commitment required of participants. This waiver would not adversely affect the rights and welfare of subjects.

Written Informed Consent: A copy of the informed consent document will be provided to potential participants after screening via e-mail or U.S. mail according to participants preference. Subjects will be asked to return a signed copy of written consent either via a scanned copy emailed to the study team or a signed copy sent to the study team through U.S. mail. Alternatively, subjects can provide Written Informed Consent through REDCap.

The informed consent will be cosigned prior to the start of the first data collection visit at the BADGER Laboratory. Each consented participant will be reminded that s/he may withdraw from the study at any time, for any reason, without any impact on his/her ongoing care.

Subject Compensation:

- On-site testing studies (in-lab or out-of-lab) with no take-home component:
    - Subjects in the Patient groups (users of prostheses or orthoses) will be paid $20 per hour to compensate for their time and travel expenses.
    - Subjects in the Non-patient group will be paid $10 per hour for laboratory sessions to compensate for time and travel expenses.
    - Subjects will be reimbursed for parking expenses (or a parking voucher will be provided).
- Long-term monitoring studies (take-home studies):
    - Subjects in the Patient groups (users of prostheses or orthoses) will be paid up to $450 total for participation, including on-site portions:
        - Up to $360 will be paid on a pro-rata basis based on how much of the study the subjects complete (at $40 per week for Orthosis users, $90 per week for Prosthesis users).
        - $90 will be paid for completion of the full study.
    - Subjects in the Non-patient group will be paid up to $150 total for participation, including on-site portions:
        - Up to $100 will be paid on a pro-rata basis based on how much of the study the subjects complete (at $25 per week).
        - $50 will be paid for completion of the full study.
    - Subjects will be reimbursed for parking expenses (or a parking voucher will be provided).
    - Payment will be processed only after all take-home equipment is returned.

Privacy and Confidentiality

Study procedures involving protected health information (e.g. the Consent process and background information gathering) will be performed in private rooms, by staff that have

received HIPAA training. Subjects may choose not to answer any questions that make them uncomfortable or that they feel violate their privacy. All subject data will be identified by a subject number.

Study data files will consist of hand notes from study personnel and computer data files. Most patient-reported outcome questionnaires will be completed on-line through a secure connection to ICTR REDCap, otherwise paper will be utilized during in-person visits. Hand notes and paper questionnaires will be scanned to electronic files and the hard copies will be destroyed. All these files will be identified only by the subject number (no personally identifying information will be associated with them). Coded data files will be available to all study team personnel on a need-to-access basis. Coded data files will be stored on a password-protected computer in the PI's laboratory or on HIPAA compliant servers such as ICTR REDCap. Coded files will also be transferred to other password-protected computers used by team personnel for data processing and publication. Subject information will not be disclosed to anyone who is not personnel on this study team without the written permission of the subject. To the extent permitted by law, subject identity and participation in this study will remain confidential.

Code key files (consent forms) will be stored only in hard copy, in a locked cabinet in the PI's locked laboratory or office (Department of Mechanical Engineering, 3034 or 3039 Mechanical Engineering Building) or in locked offices of the collaborating site at Walter Reed National Military Medical Center (for WRNMMC subjects). Each site (UW and WRNMMC) will retain the only copy of the code key for data collected at that site. Codes will be destroyed no more than 5 years after the completion of the study or the date of final data publication, whichever is later. De-identified data (de-identified after the codes are destroyed) will be kept indefinitely on computers in the laboratory or on servers, and used by the study team to address new scientific questions. De-identified data may be published to public repositories for analysis by other researchers.

We will take precautions to protect subject information from a breach of confidentiality with the use of electronic security measures (e.g., passwords). Additionally, paper files will be stored in a locked cabinet when not in use. Subject information will not be disclosed to anyone who is not key personnel on this study without the subject's written permission. To the extent permitted by law, subject identity and participation in this study will remain confidential.

Collection of sensitive information is limited to the amount necessary to achieve the aims of the Research. This information will be collected on a Health Questionnaire with additional notes through conversation as appropriate. We will record name, sex, date of birth, contact information, race and ethnicity, and relevant medical information (e.g. etiology of amputation/injury; time since amputation/injury; specifications of the prescribed device(s); functional K-level; underlying conditions; comorbidities; musculoskeletal, neurological or cardiovascular problems; vision or balance problems; problems with sensation e.g. neuropathy). These data are necessary to categorize results with respect to different subgroups of the target

population. For subjects without prostheses or orthoses, similar information will be collected, without the condition-specific aspects.

Data collected during the study itself will not be personally identifiable except through the code key, which will be kept separately under access control. It may include 3D locations of motion capture markers, measurements of contact force with the ground and other objects, electromyographic (muscle activity) signals, motion data from wearable sensors, respiratory gas exchange rate (e.g. oxygen consumption), and other common biomechanical signals.

One exception to the use of coded data will be identifiable photos or videos, for which explicit authorization will be requested during the Informed Consent process (authorization to record and to display identifiable images). Identifiable images will not be recorded if this authorization is withheld.

The other exception is location data, recorded as part of the long-term monitoring studies. These data include interpretable information about home, workplace and other frequently visited locations, which could potentially re-identify the participant. These data will be handled with special care, for example by obfuscating the location data prior to publication (e.g. moving it to a different part of the Earth). Specific procedures outlined in the "Risk to Privacy" section (below).

Location data may be tracked with a cell phone app. Such apps present a risk to privacy and confidentiality because the phone vendor and app vendor may both gain some information about the user. We will attempt to mitigate this risk by using custom apps or by creating accounts with impersonal credentials rather than the participant's personal information. However, perfect privacy with a cell phone is impossible, so participants will be informed of the risk and asked to accept or decline participation.

Study procedures involving field testing will take place in public spaces, including inside academic buildings, in the location of sensor installation (for those installed outside the lab) outdoors on the UW-Madison campus, and anywhere the participant chooses to go in long-term monitoring studies. These procedures involve the possibility of being recognized by bystanders. Subjects will be advised of this risk and will have the opportunity to accept it or decline participation during the Informed Consent process, including the elevated risk from having sensors installed in a public space. For patients, the use of lower-limb prostheses or orthoses is generally visible already, so the risk to privacy is comparable to ordinary daily life.

Only individuals involved with the study will have access to Protected Health Information (PHI), all identifying information, and all identifiable datasets, which will all be stored in locked cabinets in the PI's laboratory or office, or on password protected computer systems.

Data transmission among sites will be through secure, HIPAA-compliant Box folders or HIPAA-compliant storage through the UW Campus Computing Initiative or a DOD-authorized HIPAA-

compliant data transfer system. These systems will be accessible only to study team members and designated collaborators.

Study Procedures - General

Lower-Limb Biomechanics with Prostheses and Orthoses:

This study involves: (1) testing movement performance while wearing different lower limb prostheses, orthoses, or footwear, and (2) developing methods for evaluating this performance using wearable sensor data recorded during everyday life. Devices to be tested include lower-limb prostheses, tested with the customary prosthetic socket (for amputees) or prosthesis simulators (for intact subjects), as well as standard orthoses (for persons with drop-foot) and footwear (for intact subjects). Tasks may include: sitting, standing, walking and running at various speeds on level ground or treadmills, and walking up/down stairs and at inclines/declines and across slopes. Testing will be conducted in the UW Biomechatronics, Assistive Devices, Gait Engineering and Rehabilitation Lab (UW BADGER Lab), the UW Neuromuscular Biomechanics Lab (UWNMBL), UW McClain Athletics Lab, or the UW Research Park Clinic. In the lab, subjects will perform locomotor tasks over ground or on a moving treadmill. Some subject testing may be conducted in a normal everyday environment outside of the lab. Outside of the lab, subjects will perform some locomotor tasks over ground. These locomotor tasks will be tasks that they normally encounter in their everyday lives, such as walking and running in buildings and outdoors on pavement, grass, dirt, gravel, and other everyday surfaces such as stairs and ramps.

Individual laboratory testing sessions will last no more than 5 hours. Sessions with patient groups will require no more than 90 minutes of physical activity during each session. Sessions with non-patients will require no more than 120 minutes of physical activity. Activity limits will be adjusted to respect any more stringent recommendations reported by specific subjects.

Devices:

Subjects with amputation will use their own prostheses and/or standard commercially available prostheses (**Figure 1**). No experimental devices will be used in this study.

Subjects with drop-foot will use the Bioness L300 Go functional electrical stimulation neuro-orthoses or the Thuasne SpryStep, a standard carbon fiber orthosis (**Figure 2**).

To test prostheses on unimpaired subjects, these subjects will wear a “prosthesis simulator” system. One version is prosthesis simulator boots – rigid walking boots that immobilize the ankle similar to ski boots, with a special attachment on the bottom surface to simulate walking with a prosthetic foot. These experimental simulator boots have been used in past human research by the PI and others [18]–[21]. Other variations of a prosthesis simulator system may also be used, such as versions based on leg braces that circumvent the ankle rather than immobilizing it.

Unimpaired subjects may also test standard AFO's by wearing them with standard footwear. All standard devices will be purchased off-the-shelf. Standard custom orthoses (e.g. AFO's constructed to fit individual patients according to standardized procedures) will be constructed at the UW Health Orthotics and Prosthetics Clinic.

Biomechanically unimpaired subjects may also test wearable sensors through comparisons of different kinds of footwear.

The sensors used in the study have no action that could affect the subject, and their effects are not under investigation. They are for instrumentation only, and therefore are not investigational devices.

Instructions:

We will provide subjects with instructions for using the sensors and test devices (prostheses/orthoses/footwear). Information will include: how to turn on the sensors and test devices; how to plug in and charge any that need power; when they should or should not be used; how to keep them clean; what to do if certain problems arise; and contact information for the study team members whom subjects should contact if they have any questions or problems with the devices.

Analyses:

Movement analyses may include measurements of movement kinematics, forces acting on the limbs, and muscle behavior (electromyography, EMG). Movement kinematics may be recorded using a passive motion capture system with retroreflective markers mounted to various segments of the body, on the skin or over tight-fitting clothing. Body-mounted electrogoniometers and/or inertial sensors may be also used to record three-dimensional movement. For field tests, global positioning system (GPS) and/or bluetooth, Wi-Fi or other electronic positioning systems may record the participant's location for characterization of activities. Ground reaction forces will be recorded using force plates, a split-belt force treadmill, a load cell mounted in the prosthetic pylon, and/or pressure-sensitive shoe insoles. Electromyography (EMG) measurements will be made with electrodes placed on the skin surface to record signals from lower-extremity muscles. If EMG measurements are desired from the residual limb muscles of persons with amputation, special sockets will be fabricated by a certified prosthetist to accommodate the electrodes [22].

Figure 3: Example of a wearable respiratory gas analysis system (COSMED K5). Such a system may be used to estimate energy expenditure through indirect calorimetry.

During some locomotor tasks, we may also monitor the metabolic energy cost of locomotion using measurements of respiratory gas exchange (indirect calorimetry). Subjects will wear a mouthpiece so that we can sample their inspired and expired breath gases. These gases will be analyzed with a metabolic cart or a light-weight backpack-mounted gas analysis system to determine oxygen consumption and carbon dioxide production (e.g. **Figure 3**).

Figure 4: CAREN moving treadmill system. Such a system will be used at WRNMMC to compare laboratory vs. real-world data. A similar system with a stationary treadmill may be used at UW-Madison.

During some experiments, participants will walk on a treadmill, with (**Figure 4**) or without a virtual-reality surround screen. This test will allow comparison of standard laboratory data against data collected in a real-world environment.

During some experiments, we may also test static and dynamic balance and the coordination of sensorimotor systems using the Neurocom SMART Balance Master system [23] (**Figure 5**). This system is approved to perform a range of test on adults, all related to standing balance, including conditions that (a) move a visual surround; (b) tilt the standing surface; (c) introduce soft or firm foam under the feet; and/or require the subject to lean toward his/her limits of stability. This system includes an overhead harness that will always be used to prevent falls.

Figure 5: NeuroCom SMART Balance Master system. This system may be used to test balance and sensorimotor integration and control.

Assessments, Surveys and Feedback:

We may use a short battery of physical tests to assess each patient's mobility capabilities. The Amputee Mobility Predictor [24] is a short group of tests that give a score suitable for estimating the "K-Level" of persons with amputation. The same tests will be used in orthosis users to gauge their capacity. These tests will not be performed by healthy controls.

We use standard questionnaires to rate each patient's perceived mobility and quality of life. Surveys will be administered at the beginning of the study to gauge each subject's mobility outside the lab as well as at points during the study to gauge the impact of study interventions on mobility. For subjects with Multiple Sclerosis, questionnaires will be administered for the additional purpose of assessing the impact of impairments such as fatigue on their mobility before and during the study, and to collect information on their self-rated disease severity. The specific surveys planned are the Prosthetic Limb Users Survey of Mobility (PLUS-M) [25], [26] and the Prosthetic Mobility Questionnaire [17]. Other surveys that may be considered include: MOS Short Form 36 [27]; an NIH PROMIS physical function instrument (e.g. short form 10, 11, 20) [28]; the Locomotor Capabilities Index (LCI-5) [29]; the Prosthetic Profile of the Amputee (PPA) [30]; the Prosthetic Evaluation Questionnaire – Mobility Subsection (PEQ-MS) [15]–[17]; Activities-Specific Balance Confidence scale (ABC) [31], [32]; Socket Comfort Score [33]; the Scale for Evaluation of Rehabilitation-Participation (USER-P) [34]–[36]; the Orthotics and Prosthetics Users' Survey (OPUS) [37]; the Wong-Baker faces pain rating scale [38]; and/or the PAR-PRO participation scale [39]. Some questionnaires have sections that are irrelevant to this study; these sections may be skipped when administering the questionnaires. For the MS group, additional questionnaires will include: the Modified Fatigue Impact Scale (MFIS) [40], [41], the 12-Item Multiple Sclerosis Walking Scale(MSWS-12) [42], [43], the self-Expanded Disability Status Scale (self-EDSS) [44], [45], and the Psychosocial Impact of Assistive Devices Scale (PIADS) [46].

Finally, we will use custom questionnaires to gauge the utility of the devices under test. For the MS group, custom questionnaires will also be utilized to rate their daily fluctuations in fatigue and to communicate which shoes they utilized for the day, which is necessary as this impacts data interpretation. These questionnaires will be administered either on paper or on a computer by web form (e.g. using REDCap, Qualtrics™ or other tools compliant with HIPAA requirements). The subject code, but no other identifying information, will be collected on the form. Questions will be specific to each device or group of devices tested, because each is designed based on a different concept. Each questionnaire will be submitted for IRB review and approval prior to use with subjects.

Questions may include ratings (e.g. 0-10 ratings, visual analog scales, etc.) or rankings (e.g., best to worst, 1 to 5, etc.) of comfort, discomfort, utility, preference, pain, performance, fatigue, and specific features of the device's perceived biomechanical behavior. For example, we may ask subjects to "rate the quality of forefoot rollover movement with this prosthesis," or to "rate the severity of the mid-stance 'flat spot' you perceive with this orthosis," or "rate how comfortable would you feel relying on this device to walk along a forest trail." We will also include an optional space for open comments, because user comments provide deep insight into how these kinds of devices can be improved. The surveys will exclude sensitive questions, including but not limited to: embarrassing, damaging, personal or invasive information; information that could potentially

identify the respondent; protected health information; detailed information about any health condition or disability.

Outcome Measures

Outcomes will generally be compared using a repeated-measures design, in which each subject acts as his/her own control. This design is chosen to minimize the statistical problems caused by heterogeneity in the subject population.

- Ground Reaction Force (GRF): force applied by the body to the ground. Peak forces and shape of the force vs. time trajectory are commonly used to assess gait quality. Forces closer to "normal" are usually considered better, but this goal may not apply in persons with amputation.
- Center of Pressure (COP): location where the resultant GRF acts under the foot. Location of the COP relative to the foot or shank can characterize foot/ankle function. COP fluctuations are used to characterize standing balance. Hypotheses and intended effects on COP vary depending on the goal of a prosthesis' design.
- Joint Kinematics (ankle, knee and hip): plots of joint angle or its derivatives vs. time, and characterization of peak angles, range of motion, and variability. Kinematics closer to "normal" are usually considered better, but this goal may not apply in persons with amputation.
- Joint Moments: plots of joint moment (torque) vs time or angle, and characterization of peak moments, variability, joint quasi-stiffness, and other measures. Moments closer to "normal" are usually considered better, but this goal may not apply in persons with amputation.
- Joint Powers: plots of joint power output vs. time, and characterization of peak power and total work. Power and work closer to "normal" are usually considered better, but this goal may not apply in persons with amputation.
- Prosthesis Energy Storage and Return: Power flow into and out of a prosthesis. More is usually considered better, but nuances of mechanics can alter this goal.
- Center of Mass (COM) Mechanics: work performed by each leg on the body COM, and COM velocity fluctuations in time. Typical measurable outcomes include total quantity and asymmetry in these measures.
- Dynamic Mean Ankle Moment Arm (DMAMA): similar to a weighted average center-of-pressure, recently developed to characterize gross kinematic ankle control.
- Metabolic Energy Consumption: Measured through indirect calorimetry (oxygen

consumption, optionally carbon dioxide production), energy consumption is used to assess overall effort or physiological load in a task. Reductions in energy consumption using one device vs. another are a common goal, though exercise-related projects may be designed to cause the opposite.

- Muscle Activity: Measured through electromyography. Outcomes include the plot of EMG magnitude vs time, relative timing of peak activation with respect to movements, and integrated EMG to assess a muscle's overall load or stress.
- Balance Assessments: scores and ratings from any or all of the NeuroCom Balance Master system's standard tests (details [47]: PDF – webpage):
    - Sensory Organization Test (SOT): center of pressure fluctuations across multiple perturbations to test somatosensory, visual, and vestibular components of balance control.
    - Adaptation Test (ADT): center of pressure fluctuations when the standing surface is tilted.
    - Limits of Stability (LOS): maximal ability to lean in different directions.
    - Rhythmic Weight Shift (RWS): accuracy in controlling rhythmic leaning in different directions.
    - Weight Bearing Squat (WBS): asymmetry in weight support when standing and when squatting to 30, 60 and 90-degree knee angles.
    - Unilateral Stance (US): center of pressure fluctuations during standing on one leg
- Repeated movement paths from long-term monitoring: location as reconstructed from GPS and wearable sensor data. Paths are used to determine where and when to assess gait parameters and segment kinematics.
- Gait parameters and segment kinematics from long-term monitoring: movements of the body segments on which wearable sensors are worn. Example outcomes include speed, stride length, stride width, foot clearance, cadence, gait asymmetry, joint angles, and others.
- Survey Instrument scores: Prosthetic Limb Users Survey of Mobility (PLUS-M) [25], [26] and the Prosthetic Mobility Questionnaire [17]. Also optionally the MOS Short Form 36 [27]; an NIH PROMIS mobility instrument (e.g. short form 10, 11, 20) [28]; the Locomotor Capabilities Index (LCI-5) [29]; the Prosthetic Profile of the Amputee (PPA) [30]; the Prosthetic Evaluation Questionnaire – Mobility Subsection (PEQ-MS) [15]–[17]; Activities-Specific Balance Confidence scale (ABC) [31], [32]; the Socket Comfort Score [33]; the PAR-PRO [39], the Orthotics and Prosthetics Users' Survey (OPUS) [37]; the Wong-Baker faces

pain rating scale [38]; and/or the Utrecht Scale for Evaluation of Rehabilitation-Participation (USER-P) [34]–[36]. Scores on all of these instruments include better and worse directions.

- Custom Surveys: Custom surveys may be used, including questions adapted from the standard survey instruments, as well as questions related to specific features or behaviors of the devices under test.
- Measures of Gait and Balance Function for the Multiple Sclerosis subject subgroup: The Functional Gait Assessment [48] and 6 minute walk tests [49], [50] may be used to characterize MS-specific impairments and differences in balance, gait, and measure of fatigue observed between study interventions.

Specific Procedures – Comparing Prostheses and Orthoses using Real-World Data

Study Design:

Subjects will wear one or more movement sensors on various body segments, especially the foot, as well as means of logging location data (e.g. a GPS, Bluetooth, Wifi receiver and/or cell phone app). Subjects will wear (movement sensors) and/or carry (phone) these sensors during extended measurement periods of up to three weeks per experimental condition, for up to four conditions (prostheses, orthoses or footwear). We will combine movement and location data to identify the most-frequently-repeated paths a person takes, and finally analyze movement along these paths to identify changes in mobility performance (**Figure 6**). We will also perform standard biomechanical analyses of posture and movement in the laboratory.

NOTE: Because part of this study is the development of these methods, we may change the number of sensors, which sensors are used, how they are worn/carried, how long the take-home tests are, the devices under study, and other details of the study, within the limits approved in the *Study Procedures – General* section of this protocol.

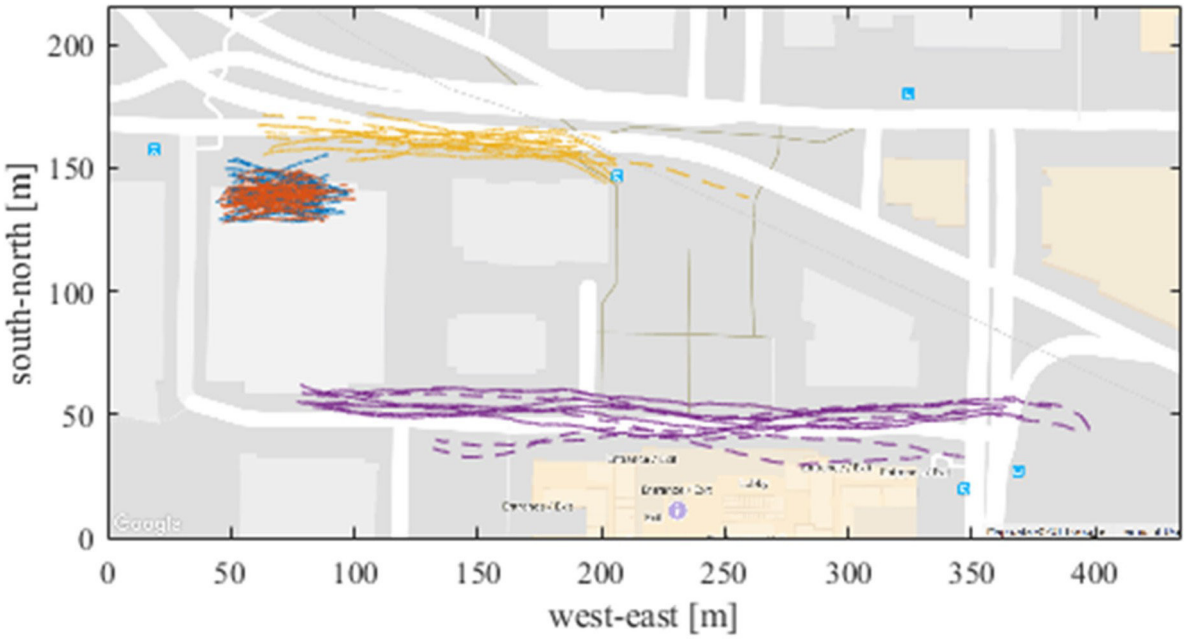

Figure 6: Example self-test by the experimenters showing highly repeated straight walking trajectories found from a 10-day walking test. The experimenter wore athletic shoes and sandals for 5 days each, indicated by solid lines and dashed lines respectively. The same color indicates same paths. Blue and red lines are walking trajectories in the hallway between the subject's office and the restroom and water fountain (different directions are separated into two different paths). Yellow lines represent the sidewalk between the building where the subject works and a nearby bus stop. Purple lines represent a sidewalk between the same building and a dining location.

Test Conditions:

- Prosthetics branch 1: Participants with amputation will use 2-4 prosthetic feet from different categories, each fit to their standard socket by a professional prosthetist.
    - Participants will use each prosthesis for a take-home test of 1-3 weeks of everyday life. Comparisons will include energy-storage-and-return prostheses (ESR) vs. prostheses with a passive hydraulic ankle (PHA) vs. prostheses with a microprocessor ankle (MPA) (**Figure 1**). Comparisons may also include Articulated ESR (AESR) prostheses, which have one or more additional joints in the mechanism, or other types of standard commercial prostheses.
    - Before and after each take-home period, participants will come to the lab for biomechanical testing and questionnaires and to be fitted with a new prosthetic foot to use for the next period.
    - The sensor systems will be worn on the affected and/or unaffected leg and foot

and/or the waist using a dedicated strap, and/or carried in a pocket or case (e.g. for data recorded by a cell phone application) throughout the study duration.

- Prosthetics branch 2: participants with amputation will use 2 or more prosthetic feet that they already own and use regularly, with only Instrumentation (sensors) added by the study team.
    - Participants will use each prosthesis for a take-home test of 1-3 weeks of everyday life. Comparisons will include a daily-use prosthesis, a running-specific prosthesis, and any other prostheses a person uses on a regular basis.
    - The sensor systems will be worn on the affected and/or unaffected leg and foot and/or the waist using a dedicated strap, and/or carried in a pocket or case (e.g. for data recorded by a cell phone application) throughout the study duration.
    - Sensors will be installed either in the lab or at an off-site location where a team member meets the subject. In such "off-site installation" situations, a designated member of the study team will meet with the participant in a public space (possibly, but not limited to, their clinician's office) to carry out the installation and validation of the take-home wearable sensors. The participants will then proceed with the take-home testing.
    - Only one lab or off-site installation visit is required to set up the wearable sensors. Sensors will be removed by the subject and returned through the mail, or alternatively the subject may come to the lab for the team to remove them.
- Orthotics branch: Participants with drop-foot will have a standard orthosis fitted by a certified orthotist, as well as the Bioness L300 Go FES neuro-orthosis. Other procedures are as above.
- Participants with no mobility impairment may use different kinds of footwear, including shoes, sandals, boots, and/or different insoles. Other procedures are as above.
- All subjects may participate in laboratory walking trials (treadmill or over-ground) to measure the detailed biomechanical effects of the different devices.

Instrumentation:

- Instrumentation may include any or all of the measurements listed in the *Study Procedures – General* section.
- Most likely measurements include: miniature inertial sensors, GPS, Bluetooth and Wifi location from a wearable receiver or cell phone app, force plate/force treadmill, EMG, motion capture, indirect calorimetry, and voice/photo/video recording.

Intended Outcome - Primary:

The primary outcome is the measured difference in stride length at identical walking speed when using different prostheses, orthoses, or footwear. We expect to observe increased stride length when using more compliant prostheses or the FES neuro-orthosis.

Intended Outcomes - Secondary:

The secondary outcomes include other measures of gait performance determined from the same system. Stride width, stride clearance, speed, stride frequency, ground reaction forces, and measures of gait regularity are among many analyses that will be performed with the data from this experiment.

Data and Safety Monitoring Plan

The PI will oversee compliance with the data and safety monitoring plan to ensure adherence to IRB guidelines. All researchers and research staff involved in the study are required to maintain Human Subjects and HIPAA training and will be continuously involved in data and safety monitoring. Data and safety monitoring will occur on a continuous basis.

Adverse events or problems will be reviewed by the principal investigator as they occur and reported to the IRB in accordance with posted guidelines at the "Events Requiring Reporting to the IRB" page: https://kb.wisc.edu/hsirbs/18324.

Data Processing/Data Analysis:

Electromyographic, kinematic, kinetic, and metabolic data will be compared with different lower limb prostheses, orthoses and footwear, using repeated measures ANOVAs. In initial experiments measuring movement performance with only the subject's own devices, we will use repeated measures ANOVAs to compare performance variables (e.g. EMG amplitude, gait economy, joint range of motion, peak ground reaction force) under different conditions (e.g. locomotion speed, incline, motor task). Corrections for multiple comparisons will be made using False Discovery Rate adjustments [51], [52]. In analysis of experimental conditions, we will use the new methods developed in this research for analyzing the same types of movement information, isolated to frequently-repeated paths in everyday life. We may also analyze specific events of interest such as slips, trips or falls that occur in everyday life and are recorded by the wearable sensors [53].

Sample size

For specific tests with a goal of publication, the sample size will be 10 participants. Studies with between 6 and 12 participants are common in the field, and have proven sufficient to

demonstrate many effects in a variety of studies of gait mechanics in persons using prostheses and orthoses [19], [54]–[61]. We estimate sample size from data on changes in gait mechanics across conditions with a past novel prosthesis [54], [56].

The sample size required per group is computed using the following formula:

$$N \text{ (per group)} = 2^* \left((z(1-\alpha/2) + z(\beta))^*\sigma/d \right)^2,$$

where d is the expected difference in outcome value, post- vs. pre-training; σ is the estimated standard deviation; **α** is the alpha error we would like to control; and β is the statistical power. Here we set a statistical goal of 80% power (β =0.80, z(β)=0.84) and α level 0.05 (z(1- α /2) = 1.96).

Based on changes gait mechanics with a past novel prosthesis, we expect: a difference in ankle push-off of 3.1 +/- 1.5 J across several conditions [54], or a difference in opposite-leg collision work of 0.055 +/- 0.04 J/kg [56]. These give sample size estimates of 4, and 9 subjects, respectively. This sample-size estimate is conservative, as it uses a two-tailed test when in fact we expect to test for specific changes (one-tailed test), and it does not account for repeated-measures structure in our experimental design. Therefore we expect 6-10 subjects to provide sufficient statistical power. We plan to use 10 subjects for the tests of prostheses and orthoses at UW Madison.

Analysis of Remotely-Collected Data

Data from UW-Madison studies, and separately from WRNMMC studies, will be analyzed at both sites, but primarily UW-Madison. Data from in-lab biomechanics studies as well as take-home studies with wearable sensors will be transmitted between sites. Personnel at both sites may be involved in analyzing the biomechanical data (movement patterns, joint loads, etc.) and interpreting the location-based data (e.g. speed, stride length, limb load) recorded from everyday life. Data transmission will use HIPAA-compliant Box folders, HIPAA-compliant folders on UW's Campus Computing Initiative (CCI) systems, or other HIPAA-compliant means approved by the DOD. Only coded data will be transmitted; each site will retain the only copy of its respective code key linking subject numbers to their direct identifiers, and the other site will not receive this information.

Potential Risks

Gait Analysis

Gait analysis uses a motion capture system and force plates to estimate the forces on the muscles and skeleton during a motion under study. Motion capture uses reflective markers that are taped or glued to the skin. Tape or glue from the reflective markers could cause skin irritation. All attempts will be made to minimize the likelihood of irritation as any irritation would influence their gait abnormally and could not be sustained for long durations. Force plates may include in-ground and treadmill-integrated versions. Risks associated with gait analysis include the

possibility of falling, or of experiencing muscle strain due to exertion. We will warn subjects that minor discomfort can be normal and that they should contact us if they are experiencing unusual muscle soreness. There is additional risk of fatigue from participation in locomotion trials. These risks are similar to everyday locomotion, but subjects will be given ample time to accommodate to different conditions before formal testing.

Falls

Walking and running inherently carry some risk of falls. These risks are similar in this study to those encountered in everyday activities. There is some elevated risk due to the effects of different devices and instrumentation on device fit and function.

Device Fit

For tests with prostheses and orthoses, there is a risk of skin irritation or abrasion due to contact between the device and the limb. The fit of any devices used will be checked repeatedly throughout the experimental sessions. Subjects using prostheses will wear their daily-use prosthetic socket, or a custom version built by a certified prosthetist, in order to ensure proper fit. For take-home tests, there is a slight increase in risk of skin irritation due to the change of equipment; subjects are asked to watch for signs of such problems and contact the research team if they occur.

For some tests (for example, EMG or respiratory gas exchange measurements), the equipment itself may be uncomfortable. This equipment will be attached to the body and adjusted as comfortably as possible, and attention will be paid to subject-specific adjustments to prevent unnecessary strain or load on the body.

Device Function

Subjects may experience minor discomfort with adjusting to the different lower-limb prostheses and orthoses. This experience often passes quickly, but subjects will be instructed to inform experimenters and stop the experiment if the discomfort is too great or too persistent.

There is a risk of malfunction whenever a device is used. With lower-limb ambulatory aids (prostheses, orthoses), malfunction could result in a fall and/or muscle strain.

Electromyography (EMG)

EMG is a tool that measures muscle activity, an important component of movement control. It uses surface electrodes to measure the electrical signals produced by muscle contractions. Risks associated with this procedure are minor and may include soreness in the areas being tested. This may last for a few days and can be relieved with an over-the-counter pain reliever. Additionally, hair at the site of each EMG electrode may need to be shaved to achieve proper electrode adhesion and conductance.

Disease Transmission:

Because the same test devices, EMG equipment, pressure insoles, and respiratory gas exchange

equipment will be used by multiple subjects, there is potential for disease transmission. This risk is reduced to an extremely small level by two mechanisms. First, subjects under treatment for infectious disease will not be allowed to participate. Second, equipment surfaces with which subjects come in contact will be disinfected following each subject's use of the equipment. The manufacturers of the test equipment items provide cleaning procedures, which will be performed between subjects. For the EMG system, this includes disinfecting the electrodes. For the respiratory gas exchange system, it involved disinfecting the mouthpiece and flow meter. The experimental devices (prostheses, orthoses) will be washed and/or disinfected with a sterilizing solution, wipe or spray. For pressure insoles and footwear, this is a shoe disinfectant and/or sanitizing wipe. Clothing will be washed between uses. Subject-specific components such as the mounting straps for the FES neuro-orthoses will be purchased new for each participant.

Risk of Being Identified:

For any tests performed outside the laboratory, the subject will be in public spaces. It is possible that someone may identify the subject during study participation. This risk is elevated compared to everyday life, as any novel devices or instrumentation will be more visible than standard prostheses or orthoses.

The risk of being identified is elevated for participants whose sensors are installed off-site in a public place. Because this involves more activity including handling multiple devices and conversing about the study, there is more occasion for the use of devices and sensors to be noticed by others. This risk will be highlighted and explicitly acknowledged by the participants in the Informed Consent process.

Risk to Privacy:

In take-home studies, location tracking and reconstruction is a critical piece of the scientific approach to analyzing frequently-repeated everyday movements. This location data can potentially expose private information such as the location of home, work and other places the participant travels to. Therefore, unaltered location data will <u>not</u> be published as a component of a public data set. Any figures or data published will have location withheld or obfuscated (such as offsetting location by a random large distance). We will remove place names, street names and building names from figures published with subjects' location data.

One of the possible means of recording location data is through use of a cell phone app that logs data. If this approach is used, it may include an additional risk to privacy because many such apps require installation on the user's real account (e.g. Google Play or Apple Store), and additional registration with the app vendor according to the vendor's terms of use. We will inform users of this risk on the Consent form and will mitigate it as outlined below in the Minimizing Risks section.

Another risk to privacy is from audio recordings in voice recordings made during everyday life. Recordings will only be made when initiated by the participant. Users will be instructed to report

only balance- and mobility-related events using voice recordings. Precautions will be taken to ensure that the privacy of non-participants is respected, including transcription by a member of the study team who will transcribe only conversation related to the study.

Another risk to privacy is from identifiable photos/videos recorded during the procedures. Explicit permission will be sought on the Informed Consent form before identifiable images are recorded.

Minimizing Risks

Subjects will be supervised at all times during the lab and field testing and will easily be able to communicate any discomfort or fatigue. Subjects will be able to take breaks whenever necessary, and may discontinue participation at any time. Subjects will be supplied with water to drink as needed. If a treadmill is used, handrails or an overhead harness will be used to prevent falls, and emergency stop buttons will also be within reach of the subject. During balance testing on the NeuroCom Balance Master system, an overhead harness will be used. During field testing, the subject's prescribed prosthesis, orthosis, or footwear, as well as any necessary tools, will be brought along by the attending experimenter, in case the need to change or remove an experimental device arises.

For take-home testing of devices, only commercially available or standard-of-care devices will be used. Subjects will be required to self-supervise, but will be given cell phone contact information for two or more members of the study team, for contact in case any difficulty arises. Subjects will be advised to keep their prescribed prosthesis and tools available, and to check regularly for discomfort or skin breakdown. A member of the study team will make weekly calls to the participants to inquire whether there are any problems with the devices, or any adverse effects.

The "take-home" portion of the study could be affected by a pregnancy that arises after initial enrollment. Because the take-home portion only uses standard commercially available devices, the risk in this case is comparable to that of ordinary life. Nevertheless, participants will be asked if they are pregnant during each weekly call, and if so they will be asked about the estimated gestation time. Subjects will be allowed to continue or discontinue participation according to their own discretion within the first 12 weeks of pregnancy. After 12 weeks of pregnancy, participation will be discontinued.

Risk of the failure in the prostheses and orthoses will be minimized through use of devices approved for patient use. Precautions will be taken to ensure safety even if the device does fail (malfunction or break), including the following:

- During all testing, subjects will be instructed to pay attention to the feel and sound of the devices and report any changes. Experimenters will also attend to device sounds and appearance. Most failures are preceded by warning signs and can be prevented

with user attention.

- During testing on a treadmill, handrails and an emergency stop button will be available within easy reach of the subject, unless an overhead harness is used.
- During over-ground laboratory or field testing, an experimenter will follow the test subject, bringing a replacement prosthesis and tools in case the prosthesis needs to be changed.
- During running trials over-ground, the subjects will wear a helmet and knee/elbow pads.
- During running trials on the treadmill, handrails or an overhead harness will be used to prevent injurious falls.

Discomfort due to energy expenditure measurement equipment will be minimized by proper adjustment of the device to fit both the face and the torso (wearable components).

Skin irritation due to motion capture markers and muscle activity electrodes will be minimized by careful placement to avoid tugging or twisting the skin. Subjects will be instructed to report any discomfort, and the test will be discontinued if there is unresolvable serious discomfort.

Physical and psychological stress due to the physical task demands will be minimized by providing appropriate rest periods between sequential trials (ca. 5 minutes). Fatigue in lab testing will be managed by ensuring no more than 6 minutes of continuous locomotion and no more than 5 hours spent in the lab in a single day. Fatigue in field testing will be managed by accompanying the subject throughout testing. In both settings, the experimenter will regularly inquire whether the subject needs rest. Fatigue in take-home testing is expected to be similar to everyday life.

Psychological stress due to perceived performance demands will be minimized by explaining the protocol in terms of doing “what you can do comfortably” (not “the best you can”), and by reiterating that the subject can stop at any time without consequence.

Audio recordings of the subject’s voice could contain private information. The following precautions will be taken to ensure appropriate privacy protections while also ensuring the necessary data are obtained:

- Voice recordings will be made on a cell phone application only when recording is activated by the participant. Files will be transferred by the participant to the study team using a USB cable upon return to the laboratory, and will be stored with the other data files. Participants will be free to delete recordings following this transfer, but will not be required to because the files record the subjects’ own voices and events.

- Voice files will be transcribed by a member of the study team, recording only information related to the event in question (editing out background and unrelated conversation).
- Voice files will not be accessible to persons outside the study team, and only transcripts will be used for public dissemination (papers, presentations).

Identifiable photos and videos will only be recorded if consent to record and show identifiable images is given by the subjects. Non-identifiable images may be recorded for analysis and for documentation and verification of the experimental procedures even if subjects decline to give permission for identifiable images.

Risk of identification in public spaces cannot be mitigated, but subjects will be informed of this risk and can withdraw if it is unacceptable. The elevated risk of identification for those in the off-site installation procedure will be included as a dedicated item in the Consent form.

Unaltered location data (a privacy risk) will not be published as a component of a public data set. Any figures or data published will have location withheld or obfuscated (such as offsetting location by a random large distance). We will remove place names, street names and building names from any figures published with location data.

Risks to privacy derived from the need to install a cell phone app will be minimized using several different techniques, to be chosen as the sensor system is finalized. First, our preferred method is to not use a cell phone at all, but rather the fully-embedded system we are designing. If we do need an app, our preferred approach is to install a custom app that is not on the Google Play store or the Apple Store. We have developed one such app in pilot testing, and installed it directly on an iOS device (but it has limitations, and we do not yet have one for Android). If instead we choose a publicly available app (due to convenience, improved features like data transmission capability, etc.), then the need to install it on the user's own Google or Apple account cannot be avoided. In this case, we will attempt to minimize exposure of personal data to the app vendor by creating an account with lab credentials such as a lab email address (e.g. "wearableSubject14@g-groups.wisc.edu", which will forward to a study team member instead of the subject). If none of these is practical or satisfactory to the subject, then the subject will be given the opportunity to refuse participation if he/she objects to installing and creating his/her own account.

Medical emergencies

Medical emergencies will be handled through standard emergency services (i.e., calling 9-1-1). Oversight will be provided by the PI or other Study Personnel in attendance during testing. Specific oversight of subjects who use prostheses or orthoses will be provided by the Certified Prosthetist or Orthotist, as related to limitations on activity and fitting of experimental devices

to avoid irritation or fall risk. Medical emergencies during take-home portions of the experiment will be handled by the participants without intervention by the study team. Subjects will be asked to report any emergency events to the Study Team for evaluation of whether the study contributed to the emergency.

Benefits

In the prosthetics study, subjects may receive temporary benefits from involvement in the study, if they find the test devices preferable to their prescribed devices. Such experiences could also provide information to help them improve their future care. No other benefits are expected for subjects involved in the prosthetics study. In the orthotics study, subjects benefit from the unusual circumstance of access to extended trial periods of two different foot-drop orthoses which may aid their decision making over which device to pursue. No other benefits are expected for subjects involved in the orthotics study.

There are significant potential scientific benefits in the prescription of proper prosthetic and orthotic technologies in patient care. Results from this study will provide documentation of motor behavior across a wide range of motor tasks in patients and unaffected subjects.

The proposed research will benefit society through:

- improving our understanding of how the different prostheses and orthotic interventions affect walking and running.
- improving clinical care by improving methods to assess mobility outcomes during real-world, everyday life

Data and Record Keeping

The PI will oversee the management of the study dataset. Data Confidentiality will be ensured by allowing only individuals involved with the study to have access to PHI, all identifying information, and all collected datasets, which will be stored in locked cabinets in the PI's Laboratory, on password protected computer systems, or on HIPAA compliant servers. Coding and de-identification of datasets have been described under the privacy and confidentiality section. Data collection methods have been described in detail in the study procedures section. Identifiable study records will be kept for five years after study completion at UW-Madison and de-identified data will be banked indefinitely.

Coded data with no direct identifiers will be transmitted using HIPAA-compliant means between the primary site at UW and collaborating scientists at WRNMMC. This data transmission is necessary to allow the collaborators to best analyze and interpret the data. Each site will retain the only copy of the code key for data collected at that site. Details of the data transmission have

been described in the Data Processing/Data Analysis section and the Privacy and Confidentiality section.

Following government policy, de-identified data may be posted on publicly accessible repositories for future analysis related to new scientific questions that can be informed by the tests performed in this research. The existing code linking data to individual subjects will be removed from any such copy of the data set, and a new code with no link will be added instead. These de-identified data are no longer “human subject data” and hence are suitable for public release.

Five years after study completion, data will be permanently de-identified. The consent forms and Health Questionnaires containing the link between codes and personal identifiers will be destroyed. These de-identified data are no longer “human subjects data” and hence will be kept indefinitely for future research use, such as re-analysis to address new hypotheses.

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