STU00208186: Personalized Mobility Interventions using Smart Sensor Resources for Lower-Limb Prosthesis Users

PROTOCOL TITLE: Personalized Mobility Interventions using Smart Sensor Resources for Lower-Limb Prosthesis Users

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1

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STUDY SUMMARY:

Investigational Agent(s) (Drugs or Devices)	None
IND / IDE / HDE #	None
Indicate Special Population(s)	☐ Children ☐ Children who are wards of the state ☐ Adults Unable to Consent ☐ Cognitively Impaired Adults ☐ Neonates of Uncertain Viability ☐ Pregnant Women ☐ Prisoners (or other detained/paroled individuals) ☐ Students/Employees
Sample Size	125
Funding Source	Department of Defense, Defense Health Program, Congressionally Directed Medical Research Programs Orthotics and Prosthetics Outcomes Research Program.
Indicate the type of consent to be obtained	☒ Written ☐ Verbal/Waiver of Documentation of Informed Consent ☐ Waiver of HIPAA Authorization ☐ Waiver/Alteration of Consent Process
Site	☒ Lead Site (For A Multiple Site Research Study) ☐ Data Coordinating Center (DCC)
Research Related Radiation Exposure	☐ Yes ☒ No
DSMB / DMC / IDMC	☐ Yes ☒ No

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OBJECTIVES:

Aim 1: Determine whether a participant's prosthesis use matches the assigned K-level and/or self-reported goals and, if not, determine the reason(s) using an expert panel to evaluate data from performance-related measures, participant-reported measures, and smartphone and prosthesis sensors (clinical toolbox.)

We will provide participants with a smartphone with the CIMON app and an unlimited data plan. We will gather three months of data from the smartphone sensors and from mc10 sensors placed on the participant's primary prosthesis and use machine-learning and data mining to establish baseline levels of prosthesis utilization, activity level, community mobility, and social interaction.

After three months, we will administer a set of standard participant-reported assessments, and a structured personal interview, and obtain K-level determination from medical records and/or prosthetic components. Clinicians and researchers from all three sites will form an expert panel to evaluate this comprehensive dataset, or clinical toolbox and determine whether each participant is achieving expected levels of community activity and meeting desired mobility goals.

Aim 2: Quantify the effects of targeted physical intervention (prosthesis repair/refit, physical rehabilitation) or psychological intervention (motivational interviewing) or both on activity levels and patient goals.

Only individuals not achieving expected and desired mobility levels, based on the expert panel evaluation, will participate in Aim 2.

We will analyze data collected in Aim 1 to determine factors limiting prosthesis use, and we will provide a targeted intervention for three months—to address physical issues (pain, poor prosthesis/socket fit repair, inadequate training, deconditioning), psychological issues (e.g., ambivalence, depression, fear of falling), or a combination of physical and psychological issues.

We will collect sensor data during the intervention, and the same toolbox of analyzed sensor data, standard assessments and participant-reported measures will be used to evaluate activity, psycho-social status, and prosthesis use. Individuals who experience an improvement in prosthesis use or goal achievement compared to baseline will be monitored for an additional three-month follow-up period with no intervention, and the same clinical toolbox of data will be gathered and used to assess maintenance of intervention benefits. Clinical toolbox data will be evaluated by the expert panel, after the intervention and follow-up periods, as described in Aim 1.

Aim 3: Identify measure(s) that sensitively predict prosthesis use to create a clinically deployable toolkit to evaluate and optimize prosthesis use in the community.

We will use data-mining and machine learning techniques to identify which standard assessments, participant-reported measures, or sensor data from our clinical toolbox most sensitively and accurately predict actual community mobility levels. This subset of measures can be deployed as a clinical toolkit to enable more accurate prediction and assessment of prosthesis use at home and in the community.

Although out of the scope of this study, in the event that the smartphone data provides the most predictive information, we will develop procedures to deploy CIMON on both iOS and Android operating systems for use by military, VA, and civilian clinics. App development at the Max Nader Center is currently supported by philanthropy and partners at Northwestern University's Center for Behavior Intervention Technologies.

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BACKGROUND:
Amputation of a limb is one of the most debilitating combat-related injuries. More than 1200 service men and women have sustained over 1700 amputations in recent and ongoing overseas conflicts [1-3]. Furthermore, 1.8 million civilians in the United States live with amputations, with an additional 185,000 new amputations occurring every year [4]. The majority of all amputations, both in military and civilian populations, occur in the lower limb. Recent statistics indicate that 41.8% of amputations due to recent and ongoing conflicts occurred at the transtibial (below knee) level, and 34.5% at the transfemoral (above knee) level [2]. Whereas service men and women who undergo combat-related amputation are typically young [5], fit, and active, nearly 90% of all civilian lower-limb amputations occur in older adults and are due to vascular disease, frequently a complication of diabetes. This population is predicted to increase [4]. The US Veteran population includes individuals with combat-related amputations from past and recent conflicts as well as older individuals, one in four of whom have a diagnosis of diabetes and thus a high risk of dysvascular amputation [6, 7].

Loss of the lower limb causes profound disability, limiting mobility, independence, and ability to pursue employment or leisure activities. The rehabilitation goal for individuals with amputations is to enable reintegration into society, employment, independent living, economic and social self-sufficiency—and for Service Members, a return to active duty and redeployment, where possible. Individual mobility goals may include performing leisure activities or the ability to attend valued social events. Non-use or reduced use of a prosthetic may limit achievement of these goals and thus lower quality of life. In addition, reduced or improper use of prosthesis may result in overuse injuries of the intact limb, or secondary injuries due to compensatory body movements. Especially for older individuals, use of prosthesis may enable independent living and community participation and prevent social isolation or further physical decline.

Although a prosthesis is the most effective treatment for limb loss, a substantial number of persons with amputations either do not use their prescribed prosthesis or do not use it to the extent expected based on their clinically predicted ability level, or Medicare Functional Classification Level (MFCL) (K-level), the rating system used by VA, military, and civilian organizations to determine eligibility for prosthetic components. Even with excellent treatment and exceptional recovery, many otherwise healthy Service Members with lower limb amputations experience difficulties in using a prosthesis [8], which limits their ability to participate in the community or pursue employment, including redeployment [9, 10]. As of December, 2017, only 25% of service members with major lower limb amputations returned to active duty, only 8% were redeployed [3], and only 26% were able to perform other high-level activities [11]. Expensive, state-of-the-art microprocessor-controlled or powered prostheses are often abandoned or not used to their full potential [12]. While documented rates of lower-limb prosthesis use vary between 49%-95% [13, 14] with an average of 7.0 to 11.5 hours use per day [15, 16], wearing a prosthesis does not correlate with activity. Step-counts for individuals with lower limb amputation are considerably lower than the recommended 10,000 steps/day or the average of 7,000-13,000 steps per day recorded for able-bodied individuals [17, 18]. Low activity levels reduce quality of life, and likely result in secondary health problems or compound existing comorbidities over the long term [19].

Many issues may limit full use of a prosthesis. Physical issues include phantom limb or residual limb pain, discomfort due to misfit of the prosthesis [8]; poor, ineffective, or inappropriate prosthetic training or physical rehabilitation; and physical deconditioning. Issues such as amputation level and etiology, comorbidities, age, or gender [20]; reinforcing factors (e.g., physical and social benefits of prosthesis use); and enabling factors [21] (e.g., ability to don the prosthesis, physical ability to walk, and use of other mobility aids [8]) affect device use. Higher

amputation levels, bilateral amputations, coronary artery disease, and residence in a nursing home all correlate with prosthesis non-use [22, 23], whereas the ability to perform activities such as walking up or down ramps, adequate dynamic standing balance, and comfort increase prosthesis use [24]. For military personnel and Veterans, other combat-related injuries, such as traumatic brain injury or multiple amputations, may affect prosthesis use. The increased energy requirements of walking with a prosthesis may also limit usage, particularly for older individuals: transfemoral amputees expend up to 60% more energy while walking than able-bodied persons [25], and the relative metabolic cost of other activities, such as sit-to-stand transitions, is even higher. Psychosocial issues include stigma associated with disability, non-acceptance of the amputation, lack of motivation or reluctance to use a prosthesis, depression, and social isolation resulting from an inability to resume former activities [26, 27]. Optimizing prosthesis use requires a quantitative understanding of multiple interacting physical and psychological pre-disposing and limiting factors.

Classification systems (such as the Healthcare Common Procedure Coding System, HCPCS, [28]) focus solely on the patient's functional abilities. Conventional methods of assessing physical mobility and daily activities of amputees include self-report (e.g., the Prosthesis Evaluation Questionnaire (PEQ) [29] or the Orthotics and Prosthetics Users Survey (OPUS) [30]) or performance measures (e.g., the six-minute walk test, the Functional Ambulation Profile (FAP) [31], and the Timed Up and Go (TUG) test [32]. However, testing within the clinic at best provides a snap-shot of potential mobility at a single time point and may be a poor representation of real-world prosthesis usage. Participant-reported questionnaires and surveys are subject to recall bias and subjective definitions of prosthesis use, and thus have poor accuracy and reliability [17]. For Service Members with high levels of physical fitness prior to injury, standard assessments are not sufficient to measure their return to previous ability levels due to ceiling effects [33]. Thus, not only do physical, social, and psychological factors limit prosthesis use [34], but clinicians lack quantitative methods to measure the effects of these factors so that they can tailor effective therapeutic intervention. While several studies have identified predictors of successful adjustments to amputation and prosthesis use, few studies have focused on identifying the prevalence of risk factors for reduced prosthesis use or evaluated the effect of interventions [23, 35-37], and very few have focused on prosthesis use in the community. Comprehensive quantification of real-world prosthesis use is a pressing issue with implications for effective rehabilitation strategies and prosthesis design.

Medicare Functional Classification Levels (MFCL), or K-levels, were established in 1995 by the US Centers for Medicare and Medicaid Services (CMS) to quantify mobility and potential benefit from prosthetic devices after lower limb loss. They have since been the designated industry standard measure of expected prosthesis use since. K-levels are assigned by physicians, based on historical health information including previous activity level, and current medical condition—including status of the residual limb and other co-morbidities; and the individual's goals. Use of standard assessments reduces subjectivity and increases accuracy [38]. The system is a rating from 0 through 4 and it indicates a person's potential to use a prosthetic device if they had a device that worked well for them and they completed rehabilitation to use the device properly. K-level assessments provide a basis for prescription and insurance coverage of prosthetic components: appropriate lower limb prosthesis is covered when the beneficiary will (I) reasonably maintain or reach the defined functional state within a reasonable period of time and (ii) is motivated to ambulate. Higher K-level designation allows provision of more technologically advanced and expensive components to allow users to achieve their ambulatory potential. However, K-levels determined by in-clinic assessments are subjective and may not reflect real world community mobility, i.e., K-level may represent capability or potential but not actual behavior [39]—elderly individuals, stroke survivors, and amputees who demonstrate relatively

high levels of ability during in-clinic assessments do not demonstrate expected levels of mobility in the community [40, 41]. While some standard assessments are correlated with K-level designations [42], and clinical measures may be used to predict prosthesis non-use [43], little information exists on how clinical measures and K-level designation correlate with community mobility levels.

Prosthesis use can be measured quantitatively using smart phones and advanced sensor technologies. Activity monitors, typically accelerometers, are routinely used to assess mobility. Various commercial triaxial accelerometers (e.g., Actigraph LLC activity monitors, Fitbit®, or Nike + Fuelband) [44-46] have been used to count steps at home and in the community. However, these devices use proprietary algorithms trained on data from healthy individuals, which can under- or over-predict performance in individuals with amputation who have different acceleration and movement profiles, leading to inaccurate step counts. A major limitation of these step-monitors is that they simply count steps without taking into consideration where the steps were taken—such as inside or outside the home, or participation in social settings, such as theatres or houses of worship. These devices also do not discriminate, for example, between the use of public transport compared to a disability services van, which may reflect an individual's ability to handle crowds or to move in locations without ramps and other accessibility services. The limited knowledge that can be derived from activity monitors is also compromised as these devices provide minimal benefit to the user and thus have a high risk of non-compliance or inconsistent use.

Smartphones, which are now carried by most adults, contain a variety of built-in sensors—including accelerometers, gyroscopes, physiological sensors, and Global-positioning Systems (GPS). Smartphones thus enable multi-modal sensing of physical, social, and psychological aspects of behavior, including mobility and physio-psychosocial status. In addition, smartphones provide phone and internet service to the user, which are built-in incentives to carry and use the device.

Building on prior work on the use and programming of smartphones by the MIT Reality Mining group [47-50], our group has built extensive expertise in machine learning and data mining, primarily focusing on multi-modal assessment of an individual's activities using smartphone-based sensors. We have designed and developed a centralized, robust, and configurable custom monitoring app—Configurable Integrated MONitoring Toolkit (CIMON) (Fig. 1), which allows download of de-identified phone sensor data to a Health Insurance Portability and Accountability Act of 1996 (HIPAA)-compliant, secure server, allowing us to mine the data for information about activity level and factors that enhance or limit mobility. CIMON provides centralized monitoring in a globally efficient system that minimizes redundancy, providing an easy-to-use application programming interface that supports a robust and configurable monitoring service. Monitoring requests may be made in several forms: (1) instantaneous requests provide an instant value for a desired metric; (2) periodic requests allow applications to receive periodic updates on the value of a metric, and (3) event notification requests allow notification when a conditional event, such as a fall, occurs. CIMON seamlessly integrates the monitoring requests of all applications using the minimum total resources and is lightweight and computationally efficient. A detailed description of the architecture and components of the efficiency engine handling the integration of sensing requests on a smartphone is available [50, 51]. CIMON passively collects sensor data, requiring little input from the user other than charging the phone and initial labeling of activities.

Smartphone-based and wearable sensor monitoring systems provide non-invasive, quantitative measures of activity and behavior outside of the clinic. Data are acquired in real time and thus are accurate and unbiased. Furthermore, we can call the participant on the smartphone to validate the data. The strength of this approach is the use of multiple sensors on the person and

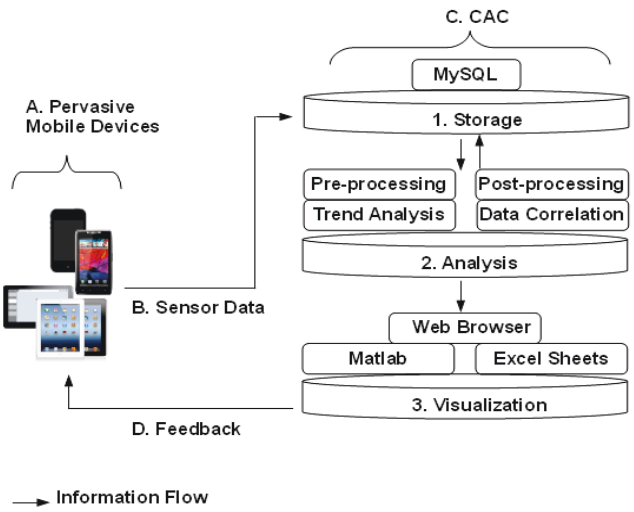
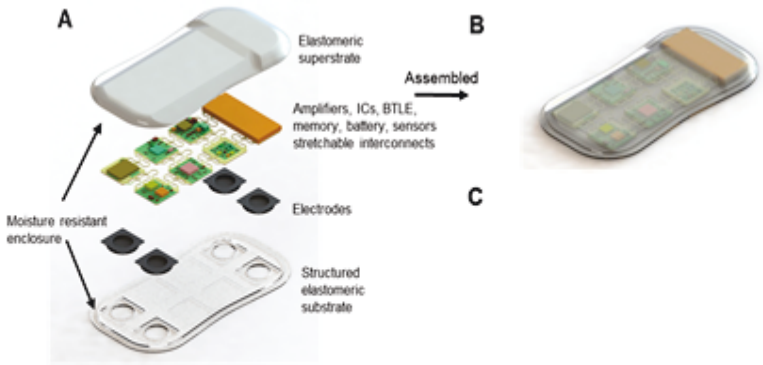


Fig. 1: *Left:* Tool kit for data collection and analysis (at the server). *Above*: Available smartphone sensors used in the CIMON app.

prosthesis to simultaneously obtain relevant data on many aspects of the participant's experience using their prosthesis. By mining data from a variety of sensors and using machine-



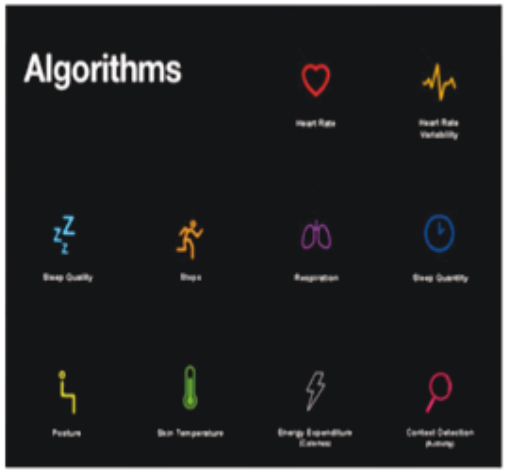


Fig. 2: *Above: MC10* Flexible sensors for data collection on the prosthesis and participant—(A) exploded view of sensor components, (B) assembled sensor. *Right*: Available algorithms for analysis of sensor data.

learning techniques to identify relevant features for comparison with measured prosthesis use, we will obtain a detailed picture of prosthesis use in the community *and* a comprehensive understanding of factors that adversely affect prosthesis use—at an individual level.

An expert panel will then evaluate all data to quantify prosthesis use. Standard performance measures and patient-reported measures predict community mobility of individuals with lower limb amputations with varying levels of accuracy. Assessments such as the Amputee Mobility Predictor (AMP [42]), Comprehensive high-activity mobility predictor (CHAMP [52]), 2-minute walk test, 5-time sit-to-stand, and PEQ may predict an individual's ability to ambulate with a prosthesis [42, 53]. However, none of these measures on their own can predict actual prosthesis use in the home and community or achievement of personal mobility and social interaction goals. Using smartphone and prosthesis-worn sensors with CIMON, together with data mining and machine-learning techniques, we can sensitively and continuously evaluate the physical, social, and psychological state of an individual with lower limb amputation. Combining information from smartphone sensors with standard assessments and participant feedback will generate a unique, rich, multi-layer and multi-factorial clinical toolbox, providing information

about daily mobility, prosthesis use, and the contributing factors that enhance or limit mobility. To evaluate this comprehensive dataset and to reach a univocal decision about each participant's activity level, we will utilize an expert panel of researchers and clinicians from the three participating sites: Walter Reed National Military Medical Center (WRNMMC), Minneapolis Veterans Administration Health Care System (MVAHCS), and The Shirley Ryan AbilityLab (SRALab, formerly the Rehabilitation Institute of Chicago), representing Military, Veteran, and civilian rehabilitation centers, respectively, who will review clinical toolbox information for each participant to determine whether prosthesis use is as expected based on K-level designation and stated mobility goals. Participants will be rated as matching their expected or desired activity level or not (i.e., a binary Yes or No decision), using a blinded two-step procedure. Combining expert opinion, outcomes data, and sensor information is the most accurate, consistent, and clinically implementable approach to cohesively combine multi-factorial datasets to determine prosthesis use in the community.

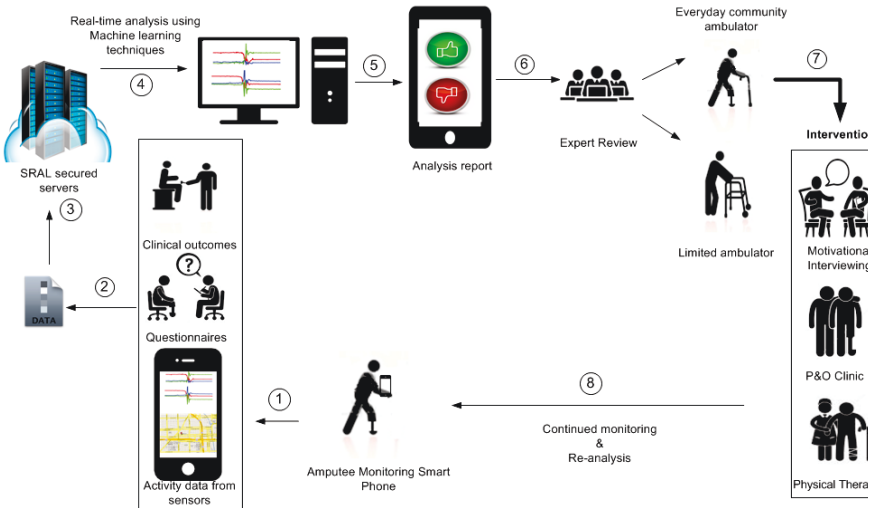


Fig. 3: Experimental Protocol, starting from a smart phone plan to data monitoring, prediction models, interventions and re-monitoring

Many clinical investigators have developed interventional strategies to promote positive behavior. Motivational interviewing (MI) is an evidence-based, participant-centered method to enhance and strengthen intrinsic motivation to change behavior. MI has been used successfully in persons with physical disabilities—including multiple sclerosis, spinal cord injury, stroke, and arthritis—to improve patient motivation and adherence to treatment; in the elderly to increase levels of physical activity [54-57]; and has been suggested as an approach to improve prosthetic usage [58]. The goal of MI is to guide an individual toward behavior change, by asking questions that allow participants to explore their reasons for making a change towards a goal and to explore and overcome reluctance or ambivalence toward achieving those goals, taking into account their level of motivation. MI methods help establish a collaborative partnership between a coach and the participant that fosters respectful evocation of the participant's perspective and autonomy to make decisions regarding their health.

We will provide individualized, tailored counseling sessions using MI techniques, based on practice guidelines specific to each study site, focused on motivation and goal setting for increased use of the participant's prosthesis in the home and community. The coach will encourage the participant to weigh all aspects of making and committing to behavior change and to take a leading role in problem solving. The participant will be asked to set personal goals that are relevant, important, and achievable using a semi-structured interview that explores facilitators and barriers to prosthesis use. Short-term goals—which could include increasing social interactions, managing residual limb pain, and reducing depressive symptoms—will be established to support the overarching long-term goal of increasing prosthesis use.

We propose a clinical trial to identify individuals who do not achieve the level of community mobility predicted by K-level and/or are not achieving personal mobility goals, identify the barriers to prosthesis use, and evaluate targeted interventions to improve prosthesis use and facilitate achievement of participants' goals (Fig.3).

We will characterize prosthetic device use based on sensor data for stepping activity, physical activity levels, and activity types, and GPS locations. We will use machine-learning methods and multivariate regression analysis to predict daily mobility with the prosthesis using measures of body structure and function, activity limitations, and demographic characteristics. We will use this data, together with standard assessments and participant-reported measures, to identify what factors or characteristics predict level of prosthesis use. For example, based on preliminary data, we expect an average daily stepping activity of 1150 for K2, 1450 for K3, 2550 for K4. For non-injured people less than 2500 steps/day is considered sedentary, 5000-7499 daily steps are considered low activity, 7500-9999 as moderately active, and above 10,000 as active. GPS data from the smartphone will be analyzed to obtain descriptive statistics of community mobility during the 3-month monitoring period. Daily measures of community mobility will measure activities similar to those used in previous studies [66, 73] including:

- Time spent stationary vs. Time spent in transit: Movement speed will be estimated from GPS data using changes in distances over time. A threshold speed will be defined to determine whether the participant is generally stationary (e.g. eating at a restaurant) or in transit (e.g. walking or riding in a vehicle). The percentage of time spent in a stationary or transit state will be computed.
- Number of locations visited: A distance-based clustering algorithm, K-means clustering [74], will be used to identify the number of places participants visit. This algorithm will be applied to data in the stationary state.
- Location variance: Variability in GPS location determined from standard deviation of latitude and longitude
- Entropy: Variability of time spent at different location clusters.
- Time spent at home: Percentage of time spent at the location cluster representing the participant's home.
- Total distance traveled: Cumulative distance traveled, determined from the distances between location data.

Expected Outcomes: Our phone applications will accurately detect and quantify home and community mobility in real time. We will be able to verify data by calling the subject or their immediate family. We expect that we will collect sufficient data over the course of the project to allow data mining and activity prediction at an individual level. We expect that the expert clinical panel will make consistent decisions on participants' ability levels based on all collected data, and that this clinical toolbox will provide valuable information on prosthesis usage and reasons for lower-than-expected usage.

STUDY ENDPOINTS:

Following consent, subject will be given a battery of baseline assessments and self-reported measures. They will be assigned a cellular device and charger, and a sensor will be placed on the most frequently used prosthesis. Participants will carry these devices on their person and data will be collected via these devices for a 3-month period (Aim 1). At the end of this period participants will return for post-study testing mirroring the original baseline assessments. Subjects will return to Shirley Ryan AbilityLab or study site if they run into any issues with use of these devices that we cannot troubleshoot via phone call.

If the participants qualify for the second leg of the study (Aim 2) they will be assigned either physical or psychologic therapy or both for an additional 3 months, with a maximum of 18-24

sessions as deemed appropriate. Data will also be recorded via assigned cellular device during this period. Outcome measure will again be repeated upon completion of study training. Participants will again be dispatched with cellular devices for a period of 3 months and will return to the study site to repeat outcome measures and return assigned devices.

PROCEDURES INVOLVED:
Subjects will be recruited from the amputee registry and the Prosthetics & Orthotics Clinic. Those who agree to participate will be asked to come to the Shirley Ryan AbilityLab Rehabilitation Technologies & Outcomes Lab.

A research assistant will conduct a structured interview with each participant to identify satisfaction with the prostheses, expectation of use, and goals for community mobility and social interaction. A transcript of the interview will be provided to the expert panel for inclusion in their review process. The interview format will be based on the PI's previous study on creating ICF model-based tool to measure mobility in individuals with lower limb amputations [70]

We will use a battery of standard assessment and participant-reported measures that assess physical function, mobility, social activities, and depression (Table 1). All measures will be available online on REDCap (Research Electronic Data Capture), a secure, web-based application for building and managing online data capture for research studies. REDCap provides a central location for data collection and storage and allows design and management of standardized forms for data collection and easy access from all study sites, facilitating review by expert panel members.

Table 1: Performance Measures and Participant-Reported Measures

Performance-based measures:
- 10 meter walk test (self-selected velocity and fast velocity)
- Six-minute walk test
- 5-times sit to stand
- 4-square step test
- Berg balance test
- Dynamic Gait Index
- Functional Gait Assessment
- Comprehensive high-activity mobility predictor (CHAMP)

Participant-Reported Measures:
- Orthotics Prosthetics User Survey (OPUS)
- Amputee Mobility Predictor (AMP)
- Modified Falls Efficacy Scale (MFES)
- Prosthesis Evaluation Questionnaire (PEQ)
- Prosthetic limb user survey of mobility PLUS-M
- Patent Reported Outcomes Measurement System (PROMIS)
  - PROMIS Bank v1.0 – Physical Function for Samples with Mobility Aid Users
  - PROMIS Bank v1.2 – Mobility
  - PROMIS Item Bank v1.0 – Depression
  - PROMIS Item Bank v2.0 – Satisfaction with Social Roles and Activities
  - PROMIS Item Bank v2.0 – Ability to Participate in Social Roles and Activities
- Community Participation Indicators (CPI)

Smartphone and mc10 sensors will provide accelerometer, gyroscope, barometer, temperature, and GPS data, which we will analyze using machine-learning algorithms previously created to compute prosthesis use, functional status, mobility, activity levels, community mobility, social interactions, and emotional status i.e. depression and satisfaction with life[59, 71]. Subjects will carry a smartphone, e.g., Samsung Galaxy S4 running Android OS 4.4.4 with the associated Hyperion 3500 mAh extended battery. These phones are equipped with up to 2.75 GHz CPUs and a sampling rate of over 100Hz. We have used these devices at the SRALab for multi-week clinical assessments of activity levels and movements in over 50

individuals with impaired mobility and for pilot data collection for this proposal. The extended internal battery life provided consistent cellular network connectivity and continuous accelerometer recordings at a 100 Hz variable sampling rate. Intensive continuous sensing on mobile devices imposes energy constraints: continuous data collection can deplete the battery within a few hours, which makes comprehensive context sensing infeasible. Therefore, we will use an adaptive sensing approach that adjusts sensing types, rates, and other parameters to ensure satisfactory battery life while providing complete and accurate context information. We will place mc10 sensors on participants' primary prostheses to obtain accurate data on device use during all measured activities.

We will ask patients to carry their phones in their pocket or on a dedicated belt, pocket, or handbag to maximize our ability to detect activities; we will automate analysis to handle recordings from phones carried in nonstandard locations. In a study including able-bodied subjects wearing a phone on a belt, or in a pocket, hand, or bag/purse) while performing varied activities (sitting, standing, sit/stand transitions, and walking) we were able to predict how the phone was being carried with 91.6% accuracy [72]. Orientation-independent features have been used to improve classification accuracy when the phone is worn in different ways. This method estimates the direction of gravity using the accelerometer signal and, in turn, the orientation of the phone, providing estimation of the vertical and horizontal components of the user's motion, which can be used to calculate orientation independent features. We will improve accuracy by instructing participants to calibrate the phone by performing a fixed set of activities in the lab and at home (e.g., walking, sit-to-stand transitions). Labeling an activity involves removing the phone from its pouch, selecting an activity label from a dropdown menu on the user interface, replacing the phone in the pouch, and performing the activity. We will incorporate each subject's preliminary labeled data into our classifiers. False positives and negatives will be used to validate the classification and improve the algorithms.

Subjects activities of daily living will not be restricted in any way. After 3 months of data collection participants will be asked to return to the Shirley Ryan AbilityLab or study site to repeat a comprehensive set of performance-related measures, participant-reported measures (See Table 1), and structured interviews to get a snapshot of current prosthesis use, assess patient satisfaction with their level of mobility, and determine their goals for mobility and social activities. A complete medical history, radiological reports, physical assessments together with socio-economic information such as living in a house or apartment, suburb or city, employed or unemployed, level of family support, will be collected. We anticipate that this initial testing will require 2-4 hours. All information will be collected, together with analyzed sensor data, into a clinical toolbox.

If prosthesis use is as expected, and the participant's mobility goals are being achieved, they will leave the study. If prosthesis use is lower than predicted, or if patient goals are not being achieved, we will mine the data to identify reasons for reduced use: physical (prosthesis fit, pain, conditioning level, device training), psychological (lack of motivation, depression, etc.), or a combination of both. These participants will continue to Aim 2 for an additional 3 months.

Interventions will be provided during a three-month period (between T_0 and T_1, Fig. 7), while smartphone and sensor monitoring continues. After three months, we will repeat all standard assessments and participant-reported measures to create a clinical toolbox to determine the effects of the intervention (via expert panel as described for Aim 1). Subjects who improve prosthesis use as a result of the intervention will be monitored and assessed three months after the end of the intervention (at T_2) in the same way, to assess maintenance of mobility or goal attainment.

Clinicians will provide the intervention using existing clinical care models at each site to minimize disruption, comply with local regulations and processes, and ensure that the intervention is clinically implementable in these and similar settings. Clinicians may deliver interventions in person or remotely, via satellite sites, outpatient centers, or through telemedicine, to minimize cost and disruption and enhance convenience for participants.

- At the VA site, participants will be assessed by the MVAHCS regional amputation center (RAC) clinicians, either at in-person or via a telehealth clinic session. A physiatrist, a physical therapist, and a prosthetist will be present at the assessment. The RAC clinicians will co-treat and provide follow-up care for any physical interventions. For a psychosocial intervention, a VA psychologist will be consulted per standard procedures.
- At the DoD site, participants will be assessed by Advanced Rehabilitation Center clinicians, including a physiatrist, a physical therapist, and a prosthetist. The clinicians will co-treat and provide follow-up care for physical interventions. For psychosocial interventions, participants will be referred to a DoD psychologist.
- At SRALab, clinician interventions will follow standard practice guidelines based on Center for Medicare/Medicaid Services recommendations, which provide a maximum of 18-24 physical rehabilitation sessions over 3 months. Counseling sessions will occur either in person or by telephone with a minimum of 13 sessions over 3 months. Participants will also meet with a physiatrist and prosthetist as needed. Interventions will be provided according to the needs of the individual; a typical timeline is described below. No cost will incur to participants for these interventions.

Physical Intervention: Individuals identified as having physical issues (poor prosthesis fit, function, comfort or physical conditioning) will receive prosthetic care and physical therapy to address these issues. This includes adjusting socket fit, component fit and repair and in some instances replacement as per clinician recommendation and reimbursement situations. Rehabilitation strategies include gait and prosthesis use retraining, balance fall-prevention, and range-of-motion training, strengthening, pain management (phantom-limb pain, low back pain, other musculoskeletal pain), and activities of daily living training, based on participant-reported mobility goals.

Individuals whose prosthesis use is reduced due to psychological issues will be provided with MI and other related psychological interventions. This intervention will begin with an individual face-to-face counseling session lasting approximately 30-45 minutes, the goals of which are to (1) establish a relationship between the coach (a person trained in motivational interviewing) and the participant; (2) perform a systematic assessment of factors that may influence wear of the participant's prosthesis; and (3) establish an individual action plan based on the results of the systematic assessment. The participant will be asked to set personal goals that he/she finds relevant, important, and achievable using a semi-structured interview that explores facilitators and barriers to wearing their prosthesis. Short-term goals will be established to support an overarching long-term goal, which could include increasing social interactions, managing residual limb pain, depression, etc. Together, the participant and coach negotiate the strategies and an action plan to help the participant achieve his/her self-identified goals to increase prosthesis wear time. The participant and coach determine a strategy to record the participant's progress. Follow-up individual intervention contacts will occur by telephone or Skype, lasting approximately 10 minutes and will include an assessment of achievement of short-term goals, assessment of long-term goals and revision of short and/or long-term goals as needed. The coach can make referrals as necessary to other members of the team to give individualized guidance as needed. Typically, at SRALab, these sessions will occur at the start of the motivational interviewing intervention in person, and then weekly by telephone for 6 sessions,

once every two weeks for 3 sessions, and then monthly for 3 sessions for a total of 13 sessions over 3 months; however, timelines and frequency of sessions may vary depending on the individual participant's needs.

Combined Intervention: Individuals who are identified as having both physical and psychological issues will be provided with both interventions simultaneously.

At the end of three months' patient will return to the Shirley Ryan AbilityLab or study site to repeat a comprehensive set of performance-related measures, participant-reported measures (See Table 1), and structured interviews to get a snapshot of current prosthesis use, assess patient satisfaction with their level of mobility, and determine their goals for mobility and social activities. A complete medical history, including physical findings and radiological reports together with socio-economic information will be repeated. We anticipate that this initial testing will require 2-4 hours.

Participants that do not show improvement at the end of this period will terminate participation in this study and will be referred to other services as necessary. These participants will return all study equipment assigned to them at this point, including but not limited to cellular device, charger, and any sensors adhered to their prosthesis and in doing so complete participation of the study at this time.

Participants which show an improvement in activity relating to assigned K-levels or self-set goals will be asked to stay enrolled for an additional 3-month period between visits T1 and T2 (Fig. 8). During this time cellular and sensor data collection will continue, no interventions will be provided. Participants may be contacted during this period via phone to perform wellness checks of labeling activities.

At the end of this period participants will return to the Shirley Ryan AbilityLab (or study site) for visit T2 (Fig. 8) and repeat all outcome and patient-reported measures (Table 1). This visit will signal the end of patient participation, all equipment assigned to participants will be returned to study site.

We will use the data collected to identify measure(s) that sensitively predict prosthesis use to create a clinically deployable toolkit to evaluate and optimize prosthesis use in the community. (Aim 3)

We will use data-mining and machine learning techniques to determine which standard assessments and participant-reported measures predict prosthesis use and community mobility, which measures are sensitive to changes in activity, and which measures correlate most strongly with K-level designation.

Outcome measure scores, including performance-based and self-reported measures, and participant characteristics will be used as input features for machine learning models. These models will attempt to classify K-level (e.g. using random forests, support vector machines, or Naïve Bayes models) and estimate community mobility (e.g. using regularized regression such as LASSO - Least Absolute Shrinkage and Selection Operator, or Elastic Net models). Classification models will be evaluated for their accuracy, sensitivity, and specificity in predicting the K-level, as compared to the ground truth determined by the expert panel. Community mobility estimates will be evaluated using the root mean squared error (RMSE) and the variance explained (adjusted R2), as compared to the ground truth determined by analysis of the GPS data. We will consider both population models (which use all participants' data to make

predictions about each individual) and personal models (which use a single participant's data to make predictions for that individual). Models will be trained and cross-validated using the leave-one-observation-out method. The classification and estimation models with the lowest errors will be used to determine the relative importance of the different input features. This will allow us to assess the outcome measures and participant characteristics that contribute most to K-level and community mobility.

We will use this information to create a clinical toolkit to predict function in the community. This information could also be used to predict which patients are likely to benefit from a specific intervention. We anticipate that different measures may be of value in different populations (VA vs. Military vs. Civilian) depending amputation etiology and level, participant age, or goals. We will also interview clinicians on the expert panels at each site to determine whether the smartphone/sensor data provided valuable information. If so, future work could focus on development of a clinically implementable smartphone app. While outside the scope of this study, we have access to philanthropic funding and collaborators who have indicated that they would develop and maintain a clinically useful app: results from this study would emphasize the clinical need and benefits of this app. We would develop the app for both Android and iOS operating systems and it would be provided free of charge to military and civilian institutions.

Outcome Measures:

1. 10 Meter Walk Test (10MWT): Assesses subject walking speed in meters per second for 10 meters. Subjects will repeat each measure 3 times at their normal self-selected walking speed and 3 times at a fast speed while still able to maintain safety.
2. Six-minute Walk Test (6MWT): The 6MWT is performed as an objective evaluation of functional exercise capacity. The 6MWT is easy to administer, well tolerated, and typically reflective of activities of daily living. The test measures the distance that the patient can walk on a flat, hard surface, indoors, in a period of 6 minutes. The walk test is patient self-paced and assesses the level of functional capacity. Patients are allowed to stop and rest during the test, however, the timer does not stop. If the patient is unable to complete the time, the time stopped is noted and reason for stopping prematurely is recorded. This test will be administered while wearing a mask to measure oxygen consumption.
3. 5-times Sit to Stand Test (5XSST): The 5 Time Sit to Stand Test is a measure of functional lower limb strength during transitional movement. The individual sits in a standard height chair (43-45 cm) and is instructed to stand up and sit down 5 times as quickly as possible. The individual is not allowed to use upper extremities to push off and is instructed to cross arms over chest if able to do so. The test is scored by measuring the time it takes to complete the 5 stands. If the patient is unable to complete all 5 stands or requires assist greater than contact guard, the test is scored as a fail.
4. 4-Square Step Test: Test of dynamic balance that clinically assesses the person's ability to step over objects forward, sideways and backwards. The test takes less than 5 minutes to administer and tests activity of daily living and motor skills.
5. Berg Balance Scale: this is a standardized 14-item objective measure of postural stability and static balance; it is an established fall predictor in adults.
6. Dynamic Gait Index (DGI): Assesses individual's ability to modify balance while walking in the presence of external demands.
7. "The FGA is a 10-item test for assessing postural stability during various walking tasks. It includes 7 of the 8 items from the original Dynamic Gait Index, and 3 new items, including "gait with narrow base of support," "ambulating backwards," and "gait with eyes closed." The FGA demonstrates excellent concurrent validity with the Berg Balance

Scale for individuals with stroke. The maximum score is 30 points; minimal detectable change for chronic stroke is 4.2 points."

8. Comprehensive high-activity mobility predictor (CHAMP): Is a performance based assessment instrument to quantify high-level mobility in service members with traumatic lower limb loss.

Patient-Reported Measures:

1. Orthotics Prosthetics User Survey (OPUS): The OPUS is a self-report questionnaire which is designed to evaluate the outcome of orthotic and prosthetic services. We will administer three of the five domains: lower limb functional measure, health-related quality of life and satisfaction with device.
2. Amputee Mobility Predictor (AMP): A tool used to predict the ambulatory potential of lower limb amputees, and measure function post-rehabilitation. It was developed to provide a more objective approach to rating amputees under the various K Classifications. The test can be performed with or without the prosthesis. The test involves activities of transfers, balance and walking.
3. Modified Falls Efficacy Scale (mFES): The mFES is self-report questionnaire consisting of 14 items which is designed to measure fear of falling in the elderly. It assesses an individual's perception of balance during activities of daily living by asking "how confident are you that you can do the following activities without falling."
4. Prosthesis Evaluation Questionnaire (PEQ): PEQ was developed specifically to provide functional outcome measures in prosthetics that are more tuned to prosthesis-related changes in quality of life. It is a self-report questionnaire containing 54 questions organized into nine functional domain scales. Each of the scales may be used individually to measure only a specific domain of interest. The PEQ has been used in a wide variety of studies and is validated.
5. Prosthetic limb user survey of mobility (PLUS-M): The PLUS-M™ is a self-report instrument for measuring mobility of adults with lower limb amputation. It has been rigorously developed using modern psychometric methodology and is intended for use in clinical practice and research. PLUS-M™ instruments are based on a set of 44 calibrated questions called an item bank. PLUS-M™ instruments measure prosthetic users' mobility (i.e., the ability to move intentionally and independently from one place to another). PLUS-M™ questions assess respondents' perceived ability to carry out actions that require use of both lower limbs, ranging from household ambulation to outdoor recreational activities. The described activities relate to two primary forms of movement, locomotion (i.e., movement in a continuous, repeatable pattern) and/or postural transitions (i.e., movement from one position to another or one type of activity to another).
6. Patient Reported Outcomes Measurement System (PROMIS): is a set of person-centered measures that evaluates and monitors physical, mental, and social health in adults and children. It can be used with the general population and with individuals living with chronic conditions. The following PROMIS assessments will be assessed:
    a. PROMIS Bank v1.0 – Physical Function for Samples with Mobility Aid Users
    b. PROMIS Bank v1.2 – Mobility
    c. PROMIS Item Bank v1.0 – Depression
    d. PROMIS Item Bank v2.0 – Satisfaction with Social Roles and Activities
    e. PROMIS Item Bank v2.0 – Ability to Participate in Social Roles and Activities
7. Community Participation Indicators (CPI): A self-reported measure that uses a scale of 0-7 days per week to assess how often a subject participates in community activities.

A research staff will be present during all testing of subjects and the experiment will be promptly stopped should any signs and symptoms of discomfort be observed. Subjects will be allowed to

take rest breaks as needed during the testing and may voluntarily withdraw from the study at any time. Finally, any adverse reactions that result from participation in this study will be documented by the principal investigator on the subject's data file and reported in writing to Northwestern's Office for Protection of Human Subjects.

Video recording and/or pictures of each participant using each prosthetic device may be taken during the training and testing sessions. These items may be used to help troubleshoot potential issues for fit or functionality of the device. They may also be used for presentations and training of other research personnel. Each Subject may choose to limit if/how these items may be used, as indicated during their Consent process.

DATA AND SPECIMEN BANKING

De-identified data will be stored indefinitely. Electronic data will be stored on secure, password protected computers and paper data will be stored in locked cabinets accessible only by authorized research personnel at the Shirley Ryan AbilityLab.

If participants give written consent to be contacted for future studies, this information will be kept separate from de-identified data files, in locked cabinets accessible only by authorized research personnel. All other information will be destroyed in accordance with HIPAA and IRB compliant guidelines.

SHARING RESULTS WITH PARTICIPANTS

Results of data collection will not be shared unless specifically requested by a participant.

STUDY TIMELINES

Subjects will participate in Aim 1 of this study for 3 months.
If participants qualify for Aim 2 they will participate for an additional 6 months as details above.

INCLUSION AND EXCLUSION CRITERIA

Participants will be contacted via the Amputee Registry and Orthotics & Prosthetics Clinics at the Shirley Ryan AbilityLab. Subjects will also be recruited at Walter Reed National Military Medical Center (WRNMMC), Minneapolis Veterans Administration Health Care System (MVAHCS).
We expect all participants to be involved with the study for a minimum of three months, while initial sensor data are collected (Aim 1). Individuals who require an intervention will be involved with the study for approximately nine months. The interventions (Aim 2) will follow clinical protocols at each study site to increase compliance, minimize disruption, and ensure that the results will be rapidly deployable. Clinical work flows may differ across sites but will be consistent within each site. Licensed psychologists will administer MI at each site, with oversight from trained MI experts. As MI protocols are dependent on individual need, no standard protocol is possible within or between sites; clinicians will document the number of sessions and patient-identified goals and strategies to enhance mobility and attain goals and we will summarize this information to guide MI deployment.

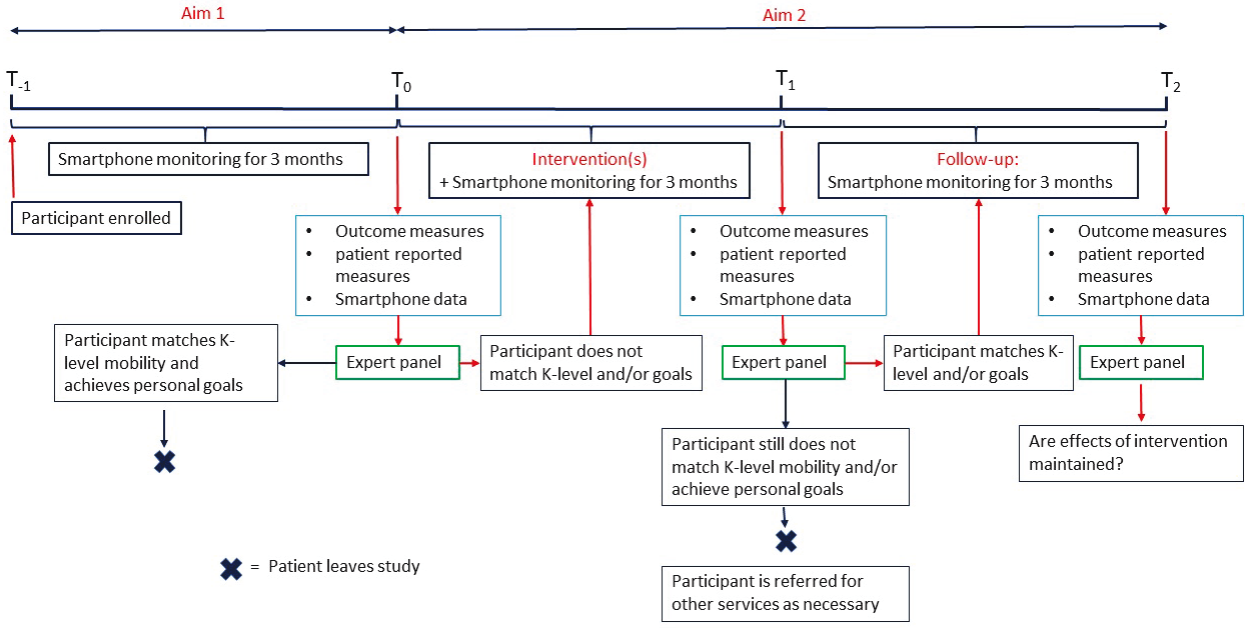
Inclusion Criteria

- Unilateral or bilateral lower limb amputation at transtibial or transfemoral level
- Ability to wear and use a prosthesis
- Designated K-level 2 – 4, or equivalent

- Prescription of definitive prosthesis
- VA participants must receive care through the VA or related remote-site clinic
- Age: 18-89 years—to reflect the age range of eligible participants at DoD and VA study sites, including young, combat-injured Service Members and healthy older Veterans, aged 70-80.

Exclusion Criteria

- Co-morbidities that limit prosthesis use, independently of prosthetic function, training, or motivation, such as stroke, obesity, severe traumatic brain injury, and neuralgia, which require interventions outside the scope of this study. Suitability to participate in the study will be determined by the individual's physician.
- Unable or unwilling to learn to use CIMON or to allow transmission of study data
- Unable or unwilling to provide informed consent
- Residing in an area with poor cell phone coverage



PARTICIPANT POPULATION(S)

Accrual Number:	Category/Group: (Adults/Children Special/Vulnerable Populations)	Consented: Maximum Number to be Consented or Reviewed/Collected/Screened	Enrolled: Number to Complete the Study or Needed to Address the Research Question
Local	Adult -Lower Limb Amputee	80	50
Study-wide	Walter Reed National Military Medical Center (WRNMMC)- Adult - Lower Limb Amputee	35	25
	Minneapolis Veterans Administration Health Care System (MVAHCS) - Adult - Lower Limb Amputee	35	25
Total:	150	150	100

RECRUITMENT METHODS

Participants will be recruited from the Shirley Ryan AbilityLab amputee registry and Orthotics and Prosthetics (O&P) Clinic based on clinician recommendations.

Flyers containing study and contact information will be displayed in the O&P Clinic to encourage recruitment. Study information will also be posted on the hospital website as required by Shirley Ryan AbilityLab guidelines.

COMPENSATION FOR PARTICIPATION IN RESEARCH ACTIVITIES

Participants will be compensated by a prepaid debit card i.e. Clincard for participating in the study. A payment of $50 will be made per each scheduled assessment (testing) visit, for the duration of their participation to offset time and travel.

Participants will also be given a cellular device equipped with an unlimited data plan for the duration of their participation in the study. Participants are required to return all study materials upon completion of study.

Participants will not incur any charges for physiatrist or prosthetics & orthotics appointments, or physical therapy and counseling sessions i.e. interventions provided in the course of this study. Participants will be compensated $20 for time and travel if they are required to travel to the Shirley Ryan AbilityLab for these sessions.

Participants will not be given results of research study unless a formal request for such results is made.

WITHDRAWAL OF PARTICIPANTS

Subjects will be withdrawn from the study only in the event of a medical event or complication (i.e. hospitalization) that may alter the inclusion/exclusion criteria or which limits the patient from safely completing the remainder of the study, or at the discretion of the PI. Subjects can voluntarily discontinue the study at any time. Participants are required to return all study materials including provided cellular device at this time.

Any participant who voluntarily withdraws will be requested to notify the Principal Investigator, Dr. Arun Jayaraman, in writing or call at 312-238-6875, if assistance is needed in this process. Information collected prior to the study discontinuation by a participant may still be used by the research team. The researchers reserve the right to discontinue study participation for any individual or for the study as a whole at their discretion.

RISKS TO PARTICIPANTS

The risks associated with study participation which include risk of breach of confidentiality, soreness during physical interventions (Aim 2), and behavioral assessments are no greater than minimal risk as defined in 45 CFR 46.102(i): “Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.”

1. Data security: One potential risk related to study participation is breach of data security with data collected from assigned cellular devices, which could potentially result in a loss of privacy of sensitive medical information. A number of steps have been taken and will be taken to maintain this risk as extremely small. In all instances, data will be kept in files that are stripped of subject identifiers, containing only subject study-ID numbers. A separate file that links subject study-ID numbers with subject identifying data will be generated and password-protected, and the password for this file will only be entrusted to core study personnel. In all cases, data and information will be kept on computers for which usage is password-protected and which are housed in a locked secure room. HIPAA compliance will remain a top priority at all times.
2. Behavioral assessments: It is possible that some respondents may experience stress or discomfort as a result of being asked about psychological symptoms or traumatic life experiences, but we believe such stress or discomfort presents no more than minimal risk. The absence of any reported reactions, in combination with a very low attrition rate in prior studies, suggests that our questions are not generating distress. In fact, we feel that the risk of distress as a result of our measures is quite low. Of course, there may still be residual distress as a result of any traumatic event patients may have experienced, but we are confident that the distress will not be TRIGGERED by our questions. In addition, our study consent and behavioral assessments will remind respondents that participation is completely voluntary, they can choose to terminate participation at any time without penalty, and that receipt of medical care is not contingent on the completion of the study. Finally, and given the number of assessments this study entails, there may be associated discomfort of fatigue while completing these assessments. However, the study-team will remain sentinel to this associated discomfort.

3. Soreness or mild discomfort from physical interventions (Aim 2): Participants may experience discomfort from donning and doffing prosthesis or from physical therapy. These side effects are no more than that which would be experienced during traditional rehabilitation training.

Given the attendant safeguards we have put in place these risks are minimal and justifiable by the information that will be gained to aid the amputee population. Nonetheless, we will remain sentinel for any indication of discomfort on the part of our participants.

POTENTIAL BENEFITS TO PARTICIPANTS

There may be no direct benefit to participants in this study. Participants with suboptimal prosthesis use based on assigned K-levels compared to data collected will be provided physical and motivational interventions for the following 3-month period (Aim 2.) Interventions will be aimed at improving physical and mental fitness to promote prosthesis use. There is potential for these interventions to improve overall quality of life in these participants.

DATA MANAGEMENT AND CONFIDENTIALITY

Statistical analysis will be performed by Masha Kocherginsky, PhD, Associate Professor of Preventative Medicine (Biostatistics) at Northwestern University.

Aim 1: Patients will be enrolled at T_{-1} (Fig. 8). We will use smartphone sensors to obtain summary measures of mobility and social activity during the three-month evaluation period. Standard assessment and participant-reported measures will be assessed at an in-person evaluation during the baseline evaluation visit (T_0). These data will be reviewed by the expert panel in a 2-stage process (as described in Research Strategy, Aim 1), which will determine whether the subject's prosthesis use does or does not match their expected or desired goals. The primary endpoint in Aim 1 will be the binary outcome of matching these goals (Yes or No). We expect 80% of the patient population across the three sites will not initially match goals, so to obtain n=100 participants for Aim 2 we will need to evaluate n=150 subjects. Accounting for a 20% attrition rate and assuming the true proportion of the patient population that does not match their goals is 80%, we can estimate this proportion with precision of $\pm 7.0\%$ (half of the 95% confidence interval).

In order to identify factors that are related to whether a participant matches their prosthesis use goals, we will first conduct univariate analysis for each outcome variable, comparing it between the n=25 patients who match vs. the n=100 subjects who do not match using t-test or the Wilcoxon Rank-Sum tests for continuous variables, and chi-squared or Fisher's exact tests for the categorical variables (e.g. ability to go to social locations). Next, we will use exploratory factor analysis to group the variables found to be significant in univariate analysis (using a liberal p-value cut-off

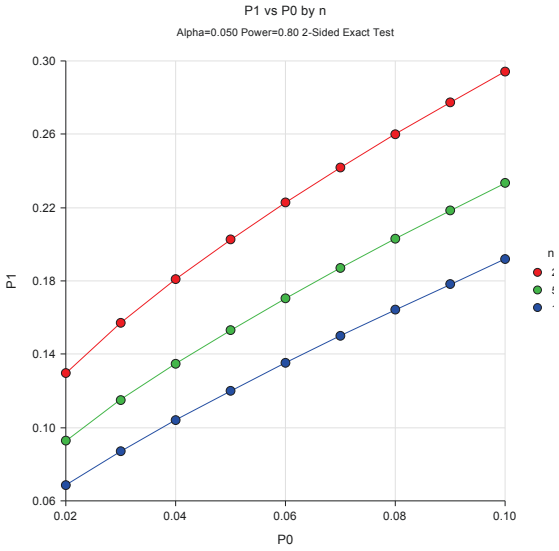


Fig. 9: Power curves for testing H_0:$p = p_0$ vs. H_1 :$p = p_1$ with 80% power and two-sided alpha=0.05 based on a one-sample exact test for proportions.

of 0.15) into several factors. These factors will then be used as predictors in a logistic regression model with the binary match (Yes or No) outcome to whether these factors, representing and interpretable as latent variables, are associated with the outcome. As a secondary analysis identifying predictors of any particular component of under-use of the prosthesis (e.g. low mobility levels, poor functional or patient-reported outcomes) will be used in a similar manner. Depending on the outcome being considered, factor analysis may be repeated using different subsets of measures so as to not overlap with the outcome being considered.

Aim 2: Participants who do not match their prosthesis use goals will be eligible for an intervention in Aim 2. The type of intervention will be recommended by the expert panel following comprehensive case review; patients will not be randomized to the different interventions. Smartphone-based monitoring will continue for 3 months, and the performance-based and participant-reported outcome measures will be repeated at an in-person evaluation during the post-intervention evaluation visit (T_1). The expert panel will review these data and again determine whether the subject matches their expected prosthesis use (Yes or No). The primary endpoint in this Aim will be the proportion of subjects who achieve "Yes" status following the intervention. We base our power calculation on a one-sample exact test of the proportion of subjects who improve, i.e., match their goals following an intervention. We expect very few subjects will improve without an intervention. With sample sizes of n=25 or 50 at individual sites and n=100 overall, we will have 80% power with alpha=0.05 (two-sided) to detect a difference between the assumed (in the absence of preliminary data) proportion p_0=5% under the null hypothesis H_0 vs. p_1=20.3%, 15.3% and 12%, respectively, under the alternative hypothesis. Fig. 9 presents detectable differences for the three sample sizes for p_0 ranging from 2% to 10%. Although there is ample power to detect small differences in the proportions of subjects who improve in the overall sample, the proposed sample size also provides adequate power to detect meaningful differences within the different populations enrolled at each site (e.g. with n=25). Even proportions as low as 12% (in the overall sample) are clinically meaningful. Changes in individual outcome measures from baseline to post-intervention will examined using paired t-test or signed rank tests for continuous measures and McNemar test for categorical variables. Linear regression models will be used to identify predictors of the outcome measure at T_1, adjusting for the baseline level. Standard regression model diagnostics will be applied, and outcome variables may be transformed to satisfy the normality assumption. In addition, factor analysis as described in Aim 1 may be used as a data reduction technique. Because these analyses are exploratory, tests will not be adjusted for multiple comparisons. Logistic regression models will be used to look at binary outcome measures in a similar fashion. Linear mixed models with repeated measures will be used to look at outcome measures across all 3 time points in a subset of patients who match their goals at T1. Such models will also allow us to appropriately model the within-subject correlation between repeated measurements (e.g. using an autoregressive variance-covariance structure). In addition, linear mixed models provide a better mechanism for handling missing data by using all available data, rather than performing a complete case analysis, if the data are assumed to be missing at random.

Aim 3: We will use similar approaches to those outlined in Aims 1 and 2, together with machine-learning algorithms, as described in the method for Aim 3.

Military Benefit and Impact:
Advances in prosthetic technology, such as powered lower limb devices and intuitive control systems, may provide superior function for Service Members and Veterans; however, achieving the potential benefits from these expensive technologies requires consistent, daily use of the

device. Despite state-of-the-art medical and rehabilitation services provided by the United States military—through Dept. of Defense (DoD) amputation care programs at Advanced Rehabilitation Centers and in the Veterans Administration (VA) Amputation system of Care, leg amputation may impose significant challenges to maintaining previous activity levels and achieving leisure, employment, and social goals. Few Service Members with major lower limb amputations return to active duty and redeployment [3]. For older civilians and Veterans, efficient use of a prosthesis may enable independent living and prevent social isolation or further physical decline. Current prosthetic assessments are based on in-clinic evaluations that do not correlate with prosthesis use in the community; many individuals do not attain expected activity levels or achieve personal mobility goals. Smartphone-based and wearable sensors provide a non-invasive, real-time monitoring system to assess prosthesis use in the home and community. Correlating actual prosthesis use and activity levels with in-clinic outcome and participant-reported measures will allow us to identify a toolkit of measures that sensitively and accurately predict prosthesis use and the barriers to optimal use. Although outside the scope of this study, this approach could be used to evaluate use of different prostheses for different activities in order to optimize DoD prescription practices to reduce costs and maximize benefits for Service Members and Veterans. A robust clinical toolkit that can be used to identify limiting factors in prosthesis use of Service members, Veterans, or civilians and allow effective relevant interventions would improve prosthesis use and quality of life, reducing the burden of amputation on the individual, their family and caregivers.

Outcome measures and session data will be collected by trained research personnel in order to ensure quality control. We will conduct an interim analysis after collecting data from 20 participants to determine if we have achieved adequate power to complete the aims of this study and re-estimate our sample size accordingly, within the limitations of the budget and timeline of the award.
Data will be collected and kept confidential in compliance with HIPAA requirements. Subjects will be assigned confidential codes for data collection. Code assignment will be kept separate from data information; subject code will be kept in a secure room under lock and key. No personal information will be stored with their data. Any data, photos or video will be stored for as long as it is deemed scientifically valuable and will be stored on a secure, password protected computer at Shirley Ryan AbilityLab. In the event this study will be published, data may be released to report the outcomes of this study. No released data will include identifiable information

Data will be uploaded automatically to a data server/database that is used for data processing, correlation, analysis, and visualization (Fig. 3). All data collected will be de-identified, encrypted, and transmitted to a HIPAA-compliant server at the Shirley Ryan AbilityLab for cloud-side analysis and interpretation. Because the GPS and movement data are Personal Health Information, we will use a HIPAA-compliant server to store de-identified sensor data and activity labels transmitted via Wi-Fi and LTE to the Shirley Ryan AbilityLab. We will run our server-side analysis code on an Ubuntu Linux virtual server on the Shirley Ryan AbilityLab VMware ESX 4.1 computer virtualization infrastructure. The system typically runs ~170 virtual machines and relies on two data centers holding 200 terabytes of patient information with periodic backups. When an activity is detected by the phone, the recent accelerometer and GPS data signals, as well as phone-based classification information, are sent to a separate virtual server. All data will be de-identified and coded to safeguard protected health information in compliance with Shirley Ryan AbilityLab HIPAA and federal privacy regulations, and data security will be monitored continuously and regulated by the Shirley Ryan AbilityLab IT security department. We will not save or transmit data with protected health information, IP addresses, or device identifiers on

the CIMON app or server. We will save date and GPS information relative to preassigned values. VA and Military staff will manage data from Veterans and Service Members, respectively, and maintain their respective cross-walk tables encoding participants' identities. We have used this approach successfully in previous studies to acquire human subject data via smartphone sensors and ensure data security.

PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF PARTICIPANTS

Every possible precaution will be taken to protect the privacy interests of subjects. To begin with participation in this is completely voluntary. Trained research personnel will explain the purpose of the study and intended use of subject's personal health information and precautions taken to keep the study information and data confidential. Subjects will be notified if any new information concerning the safety of the study becomes available which may affect their decision to remain in the study.

All personal information (names, addresses, email or phone numbers, etc.) gathered for this study that can identify participants will be kept secure to protect their privacy and will never be shared at any time with any person or entity. Data collected during the study and shared with others will reference participants only by an alphanumeric code. The "master list" linking personal information to the alphanumeric code will not be shared, and will be kept by the study PI in a secure location. All personal information linking participants to their data will be destroyed after 7 years following the completion of the study, unless the participant agrees to future contact.

COMPENSATION FOR RESEARCH-RELATED INJURY

This is a minimal risk study.

ECONOMIC BURDEN TO PARTICIPANTS

There is no anticipated economic burden to participants. A smartphone with an unlimited data plan will be provided to participants. Participants will be reimbursed for time and expenses incurred during travel to the Shirley Ryan AbilityLab.

CONSENT PROCESS

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements as approved by the Northwestern University Institutional Review Board. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form. Subjects will be consented with a new consent form if changes are made to the protocol. Prior to a patient's participation in the trial, the written informed consent form must be signed and personally dated by the patient and by the person who conducted the informed consent discussion. The consent process will take place at the Shirley Ryan AbilityLab on Floor 11 in the Rehabilitation Technologies & Outcomes Lab1401. All study sites will be required to obtain written consent prior to study participation.

QUALIFICATIONS TO CONDUCT RESEARCH AND RESOURCES AVAILABLE

This study will enroll a total of 150 participants study-wide for Aim 1, with a 20% attrition rate and an anticipated 80% enrolled exhibiting suboptimal prosthesis use and qualifying for Aim 2. Of those qualifying for Aim 2, 50 participants will be recruited from the Shirley Ryan AbilityLab, and 25 each from the Walter Reed National Military Medical Center (WRNMMC) and Minneapolis Veterans Administration Health Care System (MVAHCS). This sampling strategy ensures broad applicability to Service Members, Veterans, and civilians. We will attempt to recruit approximately equal numbers of individuals with transfemoral- and transtibial-level amputations, across sites; however, equal stratification will depend on availability of participants.

The Shirley Ryan Ability Lab houses the Center for Bionic Medicine (CBM) which is an internationally recognized research center focused on the design, control, and evaluation of multi-function prostheses for amputee patients. The CBM is a large, fully equipped facility with a research team of more than 35 staff members including physicians, prosthetists, therapists, neuroscientists, engineers, software developers, graduate students, post-doctoral researchers, and administrative staff that facilitates integration of teaching, research, and clinical knowledge.

The PI of this study, Arun Jayaraman, PT, PhD, is Director of the Max Nader Center for Rehabilitation Technologies and Outcomes (RT & O Lab), within CBM. The RT&O Lab has laboratory space of 1000 sq. ft. for clinical evaluation of patients and assessment of ambulation and certified orthotist-prosthetist function. This includes ramps, stairs, parallel bars, and other clinical evaluation equipment. This area is covered by an overhead support system such that a patient can move throughout the room and over obstacles while being safely harnessed in case of a stumble or fall. Adequate dedicated office space is available for private meetings with potential subjects, performing physical evaluations, explaining the study protocol and obtaining study consent, performing data analysis, and writing manuscripts.

The Shirley Ryan Ability Lab is a 242 bed capacity hospital, admitting a wide range of patients for comprehensive rehabilitation. It is the first of its kind in integrating research into the clinical setting by building the research labs into the clinical spaces. A subset of clinical employees from various backgrounds are hired and trained to divide time between clinical and research work.

All research personnel are required to complete IRB-compliant training and additional study specific training in compliance with standard clinical training methods to ensure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions. Subject safety will be paramount at all times; clinical oversight will be in place at all times.

STUDY-WIDE RECRUITMENT METHODS

Participants at the Shirley Ryan AbilityLab will be recruited via phone call using the amputee research registry or in person through clinician recommendation from the prosthetics and orthotics clinic. Participants can also reach out to study coordinators with information provided via flyers hung outside of the prosthetics and orthotics clinic or through the Shirley Ryan AbilityLab website in accordance with hospital guidelines.

Recruitment at other study site will use local registries or clinician recommendations.

All required approvals (initial, continuing review and modifications) have been obtained at each site (including approval by the site's IRB of record).
All modifications have been communicated to sites, and approved (including approval by the site's IRB of record) before the modification is implemented.
All engaged participating sites will safeguard data, including secure transmission of data, as required by local information security policies.
All local site investigators conduct the study in accordance with applicable federal regulations and local laws.
All non-compliance with the study protocol or applicable requirements will reported in accordance with local policy.

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