Cover Page

TITLE: **Metabolic Cost and Physical Activity in Sedentary Adults with a Unilateral Transtibial Amputation as Compared to Controls**

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HUMAN SUBJECTS PROTOCOL
University of Delaware

Protocol Title: **Metabolic Cost and Physical Activity in Sedentary Adults with a Unilateral Transtibial Amputation as Compared to Controls**

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Investigator Assurance:

By submitting this protocol, I acknowledge that this project will be conducted in strict accordance with the procedures described. I will not make any modifications to this protocol without prior approval by the IRB. Should any unanticipated problems involving risk to subjects occur during this project, including breaches of guaranteed confidentiality or departures from any procedures specified in approved study documents, I will report such events to the Chair, Institutional Review Board immediately.

1. **Is this project externally funded?** ☐ YES **X** NO

If so, please list the funding source: not applicable

2. Research Site(s)

X University of Delaware

☐ Other (please list external study sites)

Is UD the study lead? **X** YES ☐ NO (If no, list the institution that is serving as the study lead)

3. **Project Staff**
Please list all personnel, including students, who will be working with human subjects on this protocol (insert additional rows as needed):

NAME	ROLE	HS TRAINING COMPLETE?
J. Megan Sions, PhD, DPT, PT	Principal investigator	yes
Peter Coyle, DPT, PT	PhD student	yes
John Horne, CPO	Clinical partner	yes
Ryan Pohlig, PhD	Biostatistician	yes
Gregory E Hicks, PhD, PT	Senior research mentor	yes
Emma Beisheim, SPT	PhD student/student physical therapist	yes

DeJa Crippen	Undergraduate research assistant	yes
Marybeth Clancy	Undergraduate research assistant	yes
Michayla Petel	Undergraduate research assistant	yes
Daniel Awokuse	Undergraduate research assistant	yes
Melissa Capurro	PT student	yes
Nattie Chan	PT student	yes
Jefferson Cardoso, PhD, PT, MSc	Post-doctoral researcher	yes
Abdulmohsen Alroumi, BScPT, MSc	PhD student	yes
Caitlin Airey	Undergraduate research assistant	yes
Jessica Mungia	Undergraduate research assistant	yes
Erin Anderson	Undergraduate research assistant	yes
Phoebe Balascio	Undergraduate research assistant	yes
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4. **Special Populations**
Does this project involve any of the following:

Research on Children? no

Research with Prisoners? no

If yes, complete the Prisoners in Research Form and upload to IRBNet as supporting documentation

Research with Pregnant Women? no

Research with any other vulnerable population (e.g. cognitively impaired, economically disadvantaged, etc.)? please describe no

5. **RESEARCH ABSTRACT** Please provide a brief description in LAY language (understandable to an 8th grade student) of the aims of this project.

Up to 48% of adults following a lower-limb amputation will die within the upcoming year.[1] Lack of physical activity (exercise) contributes to high death rates.[2,3] It is recommended that younger (and middle-aged) adults without a health condition walk 10,000 steps/day to reduce the risk of chronic health conditions, while recommendations are 7,100 steps per day for older adults and those with chronic health conditions.[4] Adults with a lower-limb amputation walking about 21-43%[5-7] of the recommended 7,100 steps/day.[4] Step activity monitors, such as the StepWatch (a research-grade accelerometer) and the FitBit (a commercially-available monitor) provide a means of evaluating physical activity, which is important since patients tend to over-estimate their level of physical activity.[8,9] Activity monitor use, however, may not be possible in every healthcare practice setting, as monitors may cost $100-$600 and someone must remove the data from the monitor, interpret the

data, and enter the data into the patient's medical record. Therefore, physical activity questionnaires, where the patient self-reports their physical activity, are ideal in a clinical setting. Unfortunately, to date, there has been little research looking at the accuracy of physical activity questionnaires in patients with lower-limb amputations and how these questionnaires measure up to data obtained from step activity monitors.

In addition to 7,100 steps/day, adults with mobility-limiting, chronic conditions (including individuals with lower-limb amputations) should participate in ≥150 minutes of moderate-intensity physical activity per week, with activity in ≥10 minutes per bout.[4] Moderate-intensity activity has been defined as 3 metabolic equivalents (METs).[10] One MET is equal to the amount of oxygen one consumes at rest, so 3 METs means that one is consuming 3 times the amount of oxygen one would consume at rest. In healthy adults without a medical condition this equates to walking 2.6-2.7 mph[11] or 100 steps/minute[12], while for adults with an amputation of the leg below-the-knee (i.e. a transtibial amputation), 1.47 mph or 86 steps/minute has been reported to equal 3 METs.[10] Maximal walking speeds for adults with lower-limb amputations, specifically those who have lost their limb due to poor blood circulation may be ≤1.67 mph,[13-15] so one must question if walking 1.47 mph for an extended time is possible for these patients. We believe that 1.47mph is greater than 3 METs for adults with a lower-limb amputation who have other medical issues, such as diabetes and peripheral vascular disease, and who are deconditioned and not participating in physical activity.

It is important to know what speed (mph) and cadence (steps/minute) equals 3 METs in adults with a lower-limb amputation with other medical conditions who are currently inactive. We believe that these patients represent the vast majority of patients that healthcare providers encounter and must council regarding increasing their physical activity. Providers need to know what speed and cadence is equal to 3 METs for inactive patients with limb loss with other medical conditions, so that providers can appropriately advise their patients and prescribe exercise.

Walking exercise may occur over-ground or on a treadmill. When an individual with a lower-limb amputation is walking over-ground, their right-to-left side walking pattern will be more asymmetrical (uneven) when compared to when they are walking on a treadmill.[16] When walking is more symmetrical side-to-side (even), the patient may have to expend more energy. Energy expenditure can be assessed as the amount of oxygen consumed, which can be obtained while wearing a mask that evaluates your breathing while walking. Among adults with a lower-limb amputation, energy expenditure studies have generally used treadmills to look at energy expenditure.[17-20] Over-ground versus treadmill conditions, however, are different,[21] and as such, what equals 3 METs (speed, cadence) in each walking condition may vary.[22]

Further, no studies have compared the energy cost of walking in adults who are inactive with a lower-limb amputation to age-, sex-, and body mass index (computed from height and weight) - matched adults without an amputation. While studies have evaluated the impact of aging[52,53] and limb length of the amputated limb[49,51] on energy expenditure, few have evaluated modifiable factors that may impact energy expenditure among adults with lower-limb amputation.[56,57] Similarly, little research has explored modifiable factors that may impact physical activity levels.[54,55]

The project's goal is to provide knowledge that will improve physical activity prescription for inactive adults with a single, below-the-knee amputation (i.e. transtibial amputation).

Successful completion of the project may provide healthcare providers with (1) a physical activity self-report measure that can be used in clinical practice for patients with a lower-limb amputation, (2) gait speed (mph) for prescribing moderate-intensity over-ground and treadmill walking during the rehabilitation of patients with lower-limb amputations, and (3) cadence (steps/minute), for evaluating and monitoring moderate-intensity physical activity via step activity monitors, for inactive adults with a lower-limb amputation.

We will provide the first objective data that looks at the additional energy expenditure necessary for inactive adults with a lower-limb amputation who are using a prosthesis to walk short-distances as compared to able-bodied adults; this data may be used for the development of future prosthetic components that reduce energy expenditure. We will explore factors that may be linked to energy expenditure and physical activity among adults with and without a lower-limb amputation.

Specific Aim 1: Evaluate reliability and validity of physical activity self-report measures (i.e. International Physical Activity Questionnaire, Incidental and Planned Exercise Questionnaire-past week[23,24]) as compared to physical activity characteristics obtained via step activity monitors (i.e. time spent walking/day, walking bout duration, walking bouts/day) among inactive adults with a single-limb amputation (n=20).
Hypothesis**:** *H1a: Both self-report measures will have excellent test-retest reliability (ICCs ≥.75). H1b: At least 1 self-report measure will demonstrate validity with ≥ 2 physical activity characteristics.*

Specific Aim 2: Determine what gait speed (mph) and cadence (steps/minute) constitute 3 METs, i.e. moderate-intensity activity, among inactive adults with a single, below-the-knee amputation during over-ground and treadmill walking (n=20).
Hypothesis**:** *H2a: 3 METs will occur at slower speeds during treadmill walking as compared to over-ground walking. H2b: 3 METs will occur at slower cadences during treadmill walking as compared to over-ground walking.*

Specific Aim 3: Evaluate differences in energy expenditure based on oxygen consumption between inactive adults with a single, below-the-knee amputation (n=20) and matched controls (n=20) during short bouts of over-ground and treadmill walking at self-selected gait speeds, 75% and 125% of self-selected gait speeds.
Hypothesis**:** *H3: Energy expenditure will be significantly greater at all walking speeds for adults with a limb amputation as compared to controls (a) over-ground and (b) during treadmill walking (p≤0.05).*

Specific Aim 4: Explore modifiable factors that may impact energy expenditure (assessed via oxygen consumption) including comorbidities, fatigue, sleep disturbance, balance, functional lower extremity strength, functional mobility, and agility among adults with (n=20) and without a unilateral below-the-knee amputation (n=20).
Hypotheses: For both adults with and without a below-the-knee amputation (after controlling for covariates):
H4a: Comorbidities: Energy expenditure will be significantly greater at all walking speeds and for both walking conditions (over-ground and treadmill) for adults with greater comorbidity burden as assessed with the Cumulative Illness Rating Scale.
H4b: Fatigue: Energy expenditure will be significantly greater at all walking speeds and for both walking conditions (over-ground and treadmill) for adults who indicate fatigue on the PROMIS-29, as compared to those who do not indicate fatigue.
H4c: Sleep Disturbance: Energy expenditure will be significantly greater at all walking speeds and for both walking conditions (over-ground and treadmill) in adults who indicate sleep disturbance on the PROMIS-29, as compared to those who do not indicate sleep disturbance.
H4d: Balance: Energy expenditure will be significantly greater at 125% of self-selected gait speed for treadmill walking in individuals with balance deficits, as indicated by decreased Functional Reach Test distance and decreased time until loss of balance during the modified Clinical Test of Sensory Integration in Balance conditions 3 and 4 (foam, eyes open and foam, eyes closed).
H4e: Functional Lower Extremity Strength: Energy expenditure will be significantly greater for self-selected and 125% of self-selected walking speed for both walking conditions (over-ground and treadmill) in adults with decreased functional lower extremity strength, defined as slower 5 Times

Repeated Chair Rise times.
H4f: Functional Mobility: Energy expenditure will be significantly greater at for walking at 125% of self-selected speed for both walking conditions (over-ground and treadmill) in adults with decreased functional mobility, defined as increased L-test time.
H4g: Agility: Energy expenditure will be significantly greater for walking at 125% of self-selected speed for treadmill walking in adults with agility deficits, defined as slower Four Square Step Test times and Figure-of-8 Walk Test times.

We expect that relationship may be stronger among adults with a unilateral below-the-knee amputation, but we are not powered to explore between-group differences. In fact, Aim 4 (and Aim 5) is (are) exploratory, and we are looking for trends in differences.

Specific Aim 5: Explore modifiable factors that may impact physical activity, as assessed with step activity monitors, including comorbidities, balance-confidence, fatigue, sleep disturbance, balance, functional lower extremity strength, functional mobility and agility among adults with (n=20) and without a unilateral below-the-knee amputation (n=20).
Hypotheses: For both adults with and without a below-the-knee amputation (after controlling for covariates):
H5a: Comorbidities: Average daily step counts will be significantly lower for adults with greater comorbidity burden, as assessed with the Cumulative Illness Rating Scale.
H5b: Balance-Confidence: Average daily step counts will be significantly lower for adults who have lower balance-confidence per the Activities-Specific Balance Confidence Scale.
H5c: Fatigue: Average daily step counts will be significantly lower for adults who indicate fatigue on the PROMIS-29, as compared to those who do not indicate fatigue.
H5d: Sleep Disturbance: Average daily step counts will be significantly lower in adults who indicate sleep disturbance on the PROMIS-29, as compared to those who do not indicate sleep disturbance.
H5e: Balance: Average daily step counts will be significantly lower in adults with decreased Functional Reach Test distance and adults who are unable to maintain balance for 30 seconds during m-CTSIB conditions 3 and 4 (foam, eyes open and foam, eyes closed).
H5f: Functional Lower Extremity Strength: Average daily step counts will be significantly lower in adults with decreased lower extremity functional strength, defined as slower 5 Times Repeated Chair Rise times.
H5g: Functional Mobility: Average daily step counts will be significantly lower in adults with decreased functional mobility, defined as increased L-test times.
H5h: Agility: Average daily step counts will be significantly lower in adults with worse agility as indicated by slower Four Square Step Test times and Figure-of-8 Walk test times.

Specific Aim 6: Explore the relationship between gait asymmetry, as quantified by spatio-temporal and 3D kinematic parameters (e.g. cadence, stance and swing time, step length, and joint position), and energy expenditure among inactive adults with a single, below-the-knee amputation (n=20) during treadmill walking at self-selected and fast walking speeds.
Hypothesis: Energy expenditure will be greater among inactive adults with a single, below-the knee amputation who demonstrate greater side-to-side differences in walking pattern during treadmill walking at both self-selected and fast walking speeds ($p<0.05$).

Specific Aim 7: Compare side-to-side differences in walking pattern (e.g. speed, step length, and joint position) between inactive adults with a single, below-the-knee amputation (n=20) and age-matched controls (n=20) during over-ground and treadmill walking using the APDM Mobility Lab software.
Hypothesis: For both over-ground and treadmill walking conditions, inactive adults with a single, below-the knee amputation will demonstrate greater side-to-side differences in walking pattern compared to age-matched controls ($p<0.05$).

Specific Aim 8: Explore the relationship between inspiratory muscle endurance, as quantified by an individual's sustained maximal inspiratory pressure (SMIP), and energy expenditure among inactive adults with a single, below-the-knee amputation (n=20) during treadmill walking at self-selected and fast walking speeds.
Hypothesis: Energy expenditure will be greater among inactive adults with a single, below-the knee amputation who demonstrate decreased SMIP values ($p<0.05$).

Specific Aim 9: Compare differences in inspiratory muscle endurance (measured by sustained maximal inspiratory pressure, or SMIP) between inactive adults with a single, below-the-knee amputation (n=20) and age-matched controls (n=20) using the PrO_2 device.
Hypothesis: Inactive adults with a single, below-the knee amputation will demonstrate decreased SMIP values compared to age-matched controls ($p<0.05$).

Specific Aim 10: Compare differences in inspiratory muscle endurance (measured by sustained maximal inspiratory pressure, or SMIP) between inactive adults with a single, below-the-knee amputation who have low back pain compared to those who do not report pain.
Hypothesis: Inactive adults with a single, below-the knee amputation who experience low back pain will demonstrate decreased SMIP values compared to individuals with a single, below-the-knee amputation who do not have pain ($p<0.05$).

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6. **PROCEDURES** Describe all procedures involving human subjects for this protocol. Include copies of all surveys and research measures.

Overview: We propose to conduct a cross-sectional study of 22 adults with a unilateral transtibial amputation as compared to 20 sex-, age- (+/- 5 years), and body mass index- (+/- 5 kg/m^2) matched controls. This one-time session is projected to take ~ 2hours on-site at the University of Delaware on the STAR campus within the Department of Physical Therapy.

Once contact is made with potential participants, inclusion and exclusion criteria will be examined in 2 phases, first over the telephone using a structured questionnaire, and then on-site by a research team member to validate inclusion and exclusion criteria obtained by telephone. Prior to telephone screening, verbal consent will be obtained from the participant. The on-site screening will occur after individuals have signed the informed consent.

All Participants will complete a series of questionnaires that will be sent via a mailing packet prior to the on-site evaluation. Questionnaires will take about 30 minutes to complete. Questionnaires included in this **Mailing Packet** will be the:

1. Demographics Mailing Sheet: Will provide pertinent demographic information necessary for characterizing and matching participants (i.e. age, sex).
2. Medical History Checklist: We would like to have participants complete this questionnaire as it will improve the efficiency and accuracy of the Cumulative Index Rating Scale.[50] Further, it will alert the physical therapist to any relevant problems that should be consider during physical performance testing and when testing energy expenditure during the 2 walking conditions.
3. Medication Sheet: Medication review using this sheet prior to physical performance testing and testing of energy expenditure during the 2 walking conditions will enhance patient safety and allow for appropriate interpretation of vital sign responses. This sheet will also allow increased efficiency and accurate scoring for the Cumulative Illness Rating Scale regarding comorbidities.[50]
4. Activities Specific Balance Confidence Scale (ABC): The ABC is a valid[32] 16-item

questionnaire where individuals rate how confident they are that they will not lose their balance or become unsteady with various ambulatory activities on a 0-100% scale, where 0=no confidence and 100%=complete confidence.[27]

5. Patient-Reported Outcomes Measurement Information System (PROMIS-29)*:* The PROMIS-29 is a subset of the PROMIS assessment of self-reported health[29] that measures quality of life based on physical function, pain interference, fatigue, sleep disturbance, anxiety, depression, and social participation.[30,31] Individuals with lower-limb loss have been shown to score significantly lower on physical function, pain interference, and participation in social role subscales when compared to individuals without lower limb amputation.[31]
6. International Physical Activity Questionnaire – Long Form (IPAQ)*: The questionnaire, designed for adults ages 18-65, consists of 31 items assessing physical activity in four domains: transportation, work, household and gardening tasks, and leisure time.[33] It is a valid and reliable measure of self-reported physical activity level in healthy adults[34]; however, psychometric properties have not been established for use in individuals with lower-limb amputation. We will use this measure to compare self-reported physical activity levels to objective physical activity characteristics obtained from 7-days of monitoring via step-activity monitors.
7. Incidental and Planned Exercise Questionnaire-past week*:* This questionnaire has 10 items that ask about exercise type, intensity, and duration in the past week.

*These 2 questionnaires will be provided to the participant at the end of the on-site evaluation. Participants will be asked to re-complete these questionnaires at the end of their 7 days of activity monitoring and return in the envelope with the step activity monitor and activity monitor log. It is projected that re-completion of these 2 questionnaires will take < 10 minutes.

Individuals with lower-limb amputations will also complete the following:

8. Houghton Scale of Prosthetic Use[48]: The questionnaire has 4 items related to wear duration, use, and perceived stability.[28] Total scores range from 0-12 with higher scores indicating better function.[28] Scores ≥9/12 suggest the individual is a community-ambulator. This questionnaire will help to characterize the participants with limb-loss in our sample.

Questionnaires completed by participants who opt not to participate in the study (i.e. do not complete the informed consent) or who are deemed ineligible on-site will be shredded and placed in the trash (or given back to the participant to take home). This information will not be retained by the research staff. Informed consent documents will be retained in a locked file available only to research personnel. Participants will be given a copy of the informed consent for their records. Individuals with lower-limb amputations will also be asked to sign a HIPPA form. A copy of this form will be given to these research participants with a lower-limb amputation. The HIPPA form will request that the participant agree to share their medical records to allow determination of their current prosthetic components, to control for this factor during the data analysis. Specifically, we would like to control for the type of foot, passive or active and the type of suspension system, as these factors may impact energy expenditure. Only the minimal necessary information to conduct the research will be requested.

Standardized On-site Evaluation. During the on-site evaluation, a trained research team member will conduct a standardized clinical examination that will include review of questionnaires, vital signs, body anthropometric measurements, and balance and physical performance testing. Demographics information including pain and socket fit comfort score will be recorded. Patients will be asked general questions about their amputation. In the event that such questioning results in an emotional response, the examiner will refrain from further questioning that may increase participant distress. Importantly, the PI will specifically train examiners in questioning with sensitivity and role-play how to handle various emotional responses during questioning. The physical examination will include

assessment of vital signs (i.e. heartrate, blood pressure, and respiratory rate) to ensure appropriateness for participation in balance and physical performance testing and assessment of height and weight for calculation of body mass index using a medical-grade scale.

1. Cumulative Illness Rating Scale (CIRS): An index of co-morbidity burden used to quantify comorbidities based on significance of the condition and medication use; co-morbidities are a known factor related to real-world walking.[37] Administration of the CIRS will take less than 8 minutes.
2. Residual Limb Length Measurement: Residual limb length has been proven to affect energy expenditure in individuals with lower limb amputation.[49] Increased residual limb length may contribute to a decrease in the metabolic cost of walking and an increase in comfortable walking speed due to greater preservation of lower extremity muscle mass.[49] We will include this measure to allow for control of this non-modifiable covariate during energy expenditure analyses.
3. Inspiratory Muscle Endurance Measurement: To function properly, the respiratory system relies on the strength and power of the muscles responsible for breathing air into the body (i.e. the inspiratory muscles). Inspiratory muscle dysfunction, which may result from physical inactivity, major surgery, and prolonged periods of bedrest[58], may consequently reduce an individual's ability to effectively use oxygen during activity, causing a decrease in physical activity capacity and an increase in energy expenditure during physical tasks.[59] Breathing muscle endurance will be measured using the PRO_2 Hand Built device according to the Test of Incremental Respiratory Endurance (TIRE) protocol.[60] Using this protocol, participants will be asked to exhale (breathe out) as much air as possible, then breathe into a small, handheld device as hard and as long as possible. This typically lasts between 10 and 20 seconds, and real-time feedback on breathing pressure during testing will be provided through an application on a tablet. The software will generate the maximal inspiratory pressure, MIP, as well as the sustained maximal inspiratory pressure, SMIP, and duration of inspiration. These measures will be included to comprehensively assess cardiopulmonary function and relate differences in breathing muscle endurance to oxygen consumption, physical performance, and pain.
4. Physical Performance Testing
    1. Repeated Chair Stands: Individuals are asked to stand up and sit down from a chair without using their arms as quickly as possible 5 times[39]. This measure will be used as a functional assessment of lower extremity strength[40], which is a factor that may impact walking.
    2. Modified Clinical Test of Sensory Interaction in Balance (m-CTSIB): This measure assesses sensory input integration for balance maintenance when one or more sensory systems is compromised.[41]
    3. Functional Reach Test: Individuals are asked to reach forward as far as possible without moving their feet and the maximal distance reached is recorded.[42] This test has been shown to be not only reliable and valid, but to not have a floor/ceiling effect for assessment of balance among individuals with unilateral amputations like other balance measures.[42]
    4. Four Square Step Test (FSST): The FSST is a standing dynamic balance test used to assess lower extremity motor control.[43] A four-square set-up is created using canes, and participants are asked to step as quickly as possible into each square in a specific pattern, requiring steps to be taken forward, backward, and sideways to the right and left (which assesses agility).[43] A score of >24 seconds indicates increased fall risk in individuals with transtibial amputation.[44]
    5. Figure of 8 Test: A complementary test to gait speed designed to assess both straight and curved path walking ability. Individuals are asked to walk around cones to complete a "figure-of-8".[45] Time to complete the test is recorded as well as number of steps and

the participant's ability to stay close to the cones.[45] This measure will be used to assess each individual's ability to navigate tight corridors and as a test of agility.

6. L-Test of Functional Mobility: A reliable and valid[46] clinical test where participants will be asked to stand from a chair, walk 3 meters, turn 90 degrees, walk an additional 7 meters, turn 180 degrees and return to sitting in a chair.[46] This measure will be used to assess mobility, balance, turning, and walking ability (i.e. functional mobility).

Individuals with lower-limb amputations will also complete the following:

7. Amputee Mobility Predictor: This is a reliable and valid, performance-based battery that can be used to assess functional capacity of individuals with lower-limb loss who are utilizing a prosthesis.[38] Tasks include those that challenge the individual's balance, transfers, and walking. Scores range from 0-47 with use of a prosthetic device, where 47 indicates a perfect score.[38] This measure will be used to help characterize our participants with limb amputations, since this measure is universally-used in this patient population to determine functional mobility level.

Pre-Walking Set-Up

Participants will be fit with a mobile gait analysis system (APDM Mobility Lab) that will assess gait symmetry during the over-ground and treadmill walking tests that follow. Participants will be fit with APDM Mobility Lab sensors at the following locations: sternum, posterior surface of both wrists, lumbar spine, anterior surface of both thighs, anterior surface of both lower legs (and/or the sound lower leg and the prosthetic leg), and the dorsal surface of both feet (and/or the sound foot and prosthetic foot). This will take approximately 5 minutes.

The APDM software will be used to collect spatio-temporal measurements, such as stride length and velocity, as well as three-dimensional kinematic measurements, including joint position and acceleration throughout the gait cycle and maximal toe clearance during the swing phase of gait. Information regarding trunk sway and arm swing will also be collected.

Participants will also be fit with a Polar heartrate monitor, worn around the chest on the skin, to allow vital sign monitoring during the over-ground and treadmill walking conditions. The examiner will wear the wristwatch monitoring unit during the walking bouts for ease of monitoring.

Gait Speed Pre- and Post-Walking Conditions Assessment

We will use a computerized walkway system (GaitRite) to obtain self-selected (3 trials) and fast-walking speeds (3 trials) as well as other spatiotemporal parameters of gait immediately before and after each walking condition. APDM sensor data collection will also occur during self-selected and fast walking trials over the GaitRite system. By comparing pre- and post-walking gait speeds, we may be able to determine if the participant experienced fatigue during the walking bout. This will take <3 minutes per collection; there will be 4 collections total.

Metabolic Cost Testing Procedures. Participants will have their metabolic energy expenditure (i.e. oxygen consumption) measured as they walk at various speeds within the Department of Physical Therapy. Individuals with a unilateral transtibial amputation will complete the following two tests in a randomized order (controls will complete the tests in the same order as their matched participant with a unilateral transtibial amputation):

1. 3-Stage Walking Metabolic Gas Analysis on Treadmill Test: Oxygen consumption measurements will be performed with the participant walking on a treadmill, set to three different speeds. After being fitted with the metabolic gas analysis equipment, participants will sit in a chair for five minutes to collect baseline oxygen consumption. Then, participants will walk on the treadmill at a constant speed that will be derived from the participant's self-selected gait speed as measured by the GAITRite™ walkway. In stage 1, participants will walk at 75% of their self-selected gait speed for 2.5 minutes. In stage 2, participants will walk at 100% of their self-selected gait speed for 2.5 minutes. In stage 3, participants will walk at

125% of their self-selected gait speed for 2.5 minutes. These speeds were selected based on pilot data in 44 patients with a unilateral transtibial amputation who walked on average at a mean self-selected speed of .88 m/sec (95% CI: .80, .95) if they were K3 functional level and 1.16 (1.06, 1.25) if they were K4 functional level and a mean fast gait speed of 1.15 (1.05, 1.25) and 1.53 (1.38, 1.68) if they were K3 and K4 functional level, respectively. Available safety features will be used with treadmill testing (e.g. lanyards, emergency stops).

In-between stages, participants will sit until their heart rate returns below 100 beats per minute. This methodology has been derived from prior studies with similar purposes.[12, 25, 26] During each stage, the investigator will measure the number of steps taken using a hand tally counter; step cadence (i.e. steps/minute) will be computed from this value.

The Oxycon Mobile™ (CareFusion™, San Diego, CA) Portable VO2 Measurement system will be used to collect expired air via a facemask to measure VO2 uptake; this device is a lightweight, non-cumbersome machine used for portable metabolic measurement. The O2 and CO2 analyzers will be calibrated at the beginning of each test using standard calibration gases (16% O2, 4% CO2, balance nitrogen; CareFusion™, San Diego, CA). The auto calibration function will be used to calibrate volume (CareFusion™, San Diego, CA).

2. 3-Stage Walking Metabolic Gas Analysis Over-Ground Test: Oxygen consumption measurements will be performed with the participant walking over ground in an uncarpeted corridor on a course consisting of two cones, 20-meters apart. Similar to the treadmill test, participants will be asked to walk at three different speed. After being fitted with the metabolic gas analysis equipment, participants will sit in a chair for five minutes to collect baseline oxygen consumption. Then, participants will complete the walking test in three stages. In stage 1, participants will be instructed to walk at their “slow” speed for 2.5 minutes. In stage 2, participants will be instructed to walk at their “usual, comfortable” speed for 2.5 minutes. In stage 3, participants will be asked to walk at their “brisk” speed for 2.5 minutes. In between stages, participants will sit until their heart rate returns below 100 beats per minute. This methodology has been derived from prior studies with similar purposes.[12, 25, 26] Again, the Oxycon Mobile™ will be used to complete these measurements. During each stage, the investigator will measure the number of steps taken using a hand tally counter; step cadence will be computed from this value (i.e. steps/minute). Also, the distance the participant covers within each stage will be recorded.

Step Activity Monitoring.
At the conclusion of the on-site evaluation, all participants will be equipped with the StepWatch Activity Monitor. The activity monitor will be fastened near the ankle of the prosthesis using the straps included with the monitor (or in the case of controls, around the ankle joint of the right side).

Upon completion of the on-site evaluation, participants will be sent home with the activity monitor for a 7-day activity observation period. Participants will be instructed to perform their regular daily activities, wearing the monitor at all times that they are wearing their prosthesis. During the observation period, the activity monitor will record the number of steps the participants take. Participants will be provided with a pre-paid and addressed padded envelope and instructed to mail the activity monitor back after 7 days. Upon return of the monitors, study investigators will extract the step count data from the activity monitors. The 2 physical activity questionnaires will also be sent back re-completed (after 7 days) in these pre-paid envelopes, which will allow us to evaluate test-retest reliability of these questionnaires.

Review of Data. We will discuss and provide participants with blood pressure data, and physical performance data via written handouts (uploaded) at the conclusion of their on-site examination.

Participants with inappropriate vital signs will be managed in accordance with the policies outlined on the blood pressure screening handout; when necessary, the examiner will contact the provider.

7. STUDY POPULATION AND RECRUITMENT

Describe who and how many subjects will be invited to participate. Include age, gender and other pertinent information.

We will recruit 22 (males and females) with a unilateral (i.e. single limb), transtibial (i.e. below-the-knee) amputation through the UD Amputee Clinic, Independence Prosthetics-Orthotics, Inc., and from the local community using fliers (uploaded), print advertisements (uploaded), and Consent-to-Contact forms (uploaded). Given the prevalence of amputations is greater in males, we expect that the sample will be predominantly male, but we will have no inclusion/exclusion criteria related to sex. Specifically, patients with unilateral transtibial amputations who receive services at Independence Prosthetics-Orthotics, Inc. or through the UD Amputee Clinic will be supplied a Consent-to-Contact form. This form will include contact information (first and last name; telephone numbers; best time to call) that will be faxed/emailed/placed in a folder for Dr. Sions if they are interested. Dr. Sions will facilitate a phone screening of the individual after supplying the participant with additional study information (see verbal recruitment script). Information from individuals who are ineligible or who opt not to participate after the phone screen or after receiving additional study information will be shredded.

We will also contact individuals with unilateral transtibial amputations who have previously signed consents to be re-contacted for research purposes while receiving services at the University of Delaware Physical Therapy Clinic. We will utilize the verbal script for recruitment (uploaded) in these cases.

20 controls will be recruited as age-, sex-, and body mass index-matched controls.

Telephone screening will be used to determine preliminary eligibility and information will be reviewed on-site (telephone screen uploaded).

Inclusion Criteria: All Participants

1. *English-speaking and -reading*: Due to lack of feasibility of conducting evaluation in other languages.
2. *Ages 18-60 years*: Adults > 60 years may have age-related changes in energy expenditure with walking. Children under 18 years may still be experiencing limb growth and maturation that effect walking.
3. Saltin-Grimby Physical Activity Level[47] of I or II: Goal is to sample individuals who are sedentary rather than presently active.

Inclusion Criteria: Individuals with Below-the-Knee Amputations

1. *Below-the-knee amputation*: Individuals with above-the-knee amputations are known to expend greater energy when walking than those with longer residual limbs.
2. *Currently wearing a prosthesis with use of an assistive device no greater than a cane*: Necessary for proposed testing.
3. *Wearing prosthetic at least 8 hours per day and inside and outside the home*: This criteria will help to ensure that we capture adults who are beyond the initial weaning into a prosthetic and who are prosthetic users rather than nonusers.

Inclusion Criteria: Controls

1. *Pain-free in the legs and low back regions:* Pain in these regions could be a confounding variable for the proposed testing.
2. *Walk without assistive device:* Goal is to capture able-bodied individuals for comparison

purposes.

Attach all recruitment fliers, letters, or other recruitment materials to be used. If verbal recruitment will be used, please attach a script. Uploaded

Describe what exclusionary criteria, if any will be applied.

Exclusion Criteria: All Participants

1. *Current infections/illnesses*: May affect O2 consumption with walking, physical activity, and/or performance testing.
2. *Significant cardiovascular, neurological, or pulmonary condition*: Such conditions may affect O2 consumption, physical activity, and/or performance testing.
3. *Uncontrolled blood pressure or diabetes*: It may not be safe for these adults to participate in exercise testing.

Exclusion Criteria: Individuals with Below-the-Knee Amputations

1. *Amputation of sound limb*: We will exclude individuals with bilateral amputations, which is a known contributor to increased energy expenditure and impaired balance.
2. *Current issues with residual limb affecting ability to walk or for which individual is receiving treatment (i.e. open skin lesion, physical therapy for initial gait training with new prosthetic) or has weight-bearing restriction*.

Describe what (if any) conditions will result in PI termination of subject participation.

Termination of participation would only occur under a circumstance in which it became clear that the participant could not participate in a safe manner, such as unstable or abnormal vital signs or significant balance impairments resulting in questionable safety, particularly with balance testing, physical performance testing, or treadmill testing.

8. **RISKS AND BENEFITS**

List all potential physical, psychological, social, financial or legal risks to subjects (risks listed here should be included on the consent form).

In your opinion, are risks listed above minimal* or more than minimal? If more than minimal, please justify why risks are reasonable in relation to anticipated direct or future benefits.

(*Minimal risk means the probability and magnitude of harm or discomfort anticipated in the research are not greater than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests)

Minimal risks to the subjects are expected. The risks of the testing might include soreness and a temporary increase in skin, muscle, or joint pain. A small risk of a fall during balance testing, physical performance testing, and walking assessments is present. Participants will be free to withdraw from participating in the study at any time if they are uncomfortable with any of the procedures. Although no other risks or changes in the existing minimal risks are anticipated, participants will be informed if any new information arises regarding risks of participation that may affect their decision to continue in the study.

What steps will be taken to minimize risks?

To minimize soreness risks, participants will be asked to complete the minimal number of trials necessary to familiarize individuals with the testing equipment and assessment procedures and obtain a valid test. For balance, physical performance, and walking tasks, participants will be

appropriately supervised by a research member trained in participant guarding to minimize fall risk. The PI will be available by phone during all data collections. The testing done within the context of this study is used on a daily basis in the clinical setting, except that patients typically do not receive assessment of O2 consumption during walking.

Describe any potential direct benefits to participants.
Investigators will review results of blood pressure screening with each participant and review the results of each participants' functional performance testing. If the vital sign screening indicates a need for an immediate referral, the examiner will contact the primary care provider and the patient will not be eligible to participant in further testing. Participants will be given blood pressure screening and physical performance handouts to share with their medical providers.

Describe any potential future benefits to this class of participants, others, or society.
Potential benefits include establishment of speed (mph) and cadence (steps/min) for sedentary adults with lower-limb amputations that corresponds to 3 METs, i.e. moderate-intensity physical activity, which may be used when initiating an exercise program to enhance physical activity. It is possible that a physical activity questionnaire will be found to be reliable and valid for this patient population for assessment of physical activity, which will aide clinicians in evaluation of patients with limb loss. Objective data assessing the additional energy expenditure necessary for inactive adults with a lower-limb amputation to walk short-distances using a prosthesis may provide useful information for the development of future prosthetic components to reduce energy expenditure. Preliminary data evaluating modifiable factors related to energy expenditure and physical activity may help to inform future research studies.

If there is a Data Monitoring Committee (DMC) in place for this project, please describe when and how often it meets.

As this is a small project, there will not be a data monitoring committee. The Principal Investigator (Dr. Sions) will provide ongoing review of the accrued research data to ensure the safety of research participants and the provisions for protecting the privacy of participants and the confidentiality of research data.

Dr. Sions, if not present during the on-site evaluations, will be made aware of any unexpected or adverse events immediately via phone. If an adverse event occurs, it will be reported immediately by a Principal Investigator to the University of Delaware Institutional Review Board (IRB) in accordance with the IRB's stated policy for reporting adverse events in the IRB reference manual.

The Principal Investigator will review subject recruitment and accrual with the research personnel conducting phone screenings on a monthly basis. The validity and integrity of the research data will be reviewed quarterly by the Principal Investigator. Ongoing review of scientific literature, related to the research will be performed by the Principal Investigator, to determine if changes to the study should be made given new information.

9. **COMPENSATION**
Will participants be compensated for participation?
Yes

If so, please include details.
Compensation will be provided to all participants for their time and participation in the study after the individual returns the electronic monitor(s) as monitor replacement costs exceed the $40 honorarium that will be given to participants. Compensation was determined based upon the time required for evaluation and wearing the step activity monitor for 7 days, as well as travel expenses to the onsite

evaluation. If participants do not complete all questionnaires and components of the on-site examination and 7-day activity monitoring, e.g. they complete some components but choose not to complete other components or they wear the monitor for less than 7 days, then their compensation will still be $25 (assuming that the activity monitor(s) is/are returned).

10. **DATA**

Will subjects be anonymous to the researcher? No

If subjects are identifiable, will their identities be kept confidential? (If yes, please specify how)

Consent to contact forms, telephone demographics sheets, informed consent forms, and a copy of the participant's handouts will be secured in locked cabinets within the Department of Physical Therapy and will accessible only to research personnel. Names and contact information will be entered into an electronic database that will be stored on a password protected University maintained sever with regular and secured back-ups. A separate electronic database with the participant's name and contact information will be stored on a password protected University maintained server with regular and secured back-up if he/she agrees to be contacted for future studies.

How will data be stored and kept secure (specify data storage plans for both paper and electronic files. For guidance see http://www.udel.edu/research/preparing/datastorage.html)

All paper research records will be maintained in the Department of Physical Therapy (540 S. College Ave). Paper files will be secured in locked cabinets. De-Identified data will be entered from the paper records to a computerized database where all patients will be identified by a code number only. Research information will be indefinitely stored using a coded number. Only research personnel will have access to this data. There will be a single file linking participant name to number, which will be password protected and stored on a secured server, where only research members have access. Coded electronic data will be securely stored on a password-protected departmental server, as well as portable electronic devices that are securely stored in locked cabinets within the Department of Physical Therapy.

How long will data be stored? Data will be stored indefinitely.

Will data be destroyed? ☐ YES X NO (if yes, please specify how the data will be destroyed)

Will the data be shared with anyone outside of the research team? ☐ YES X NO (if yes, please list the person(s), organization(s) and/or institution(s) and specify plans for secure data transfer)

How will data be analyzed and reported?

Analyzed
Analyses will be performed using SPSS statistical software packages with consultation of an experienced biostatistician (when needed). Descriptive statistics will be used to characterize the study sample.

Specific Aim 1: To determine reliability, intra-class correlation coefficients (ICCs) with 95% confidence intervals (CIs) will be calculated to evaluate test-retest reliability of physical activity

questionnaires. To evaluate validity between the self-report questionnaire data and activity-monitor obtained data that is continuous (e.g. steps/day, total activity in minutes/day), we will use ICCs with 95% CIs. We will quantify the relationship between the self-report data and activity-monitor data using Spearman's correlation coefficients. Interpretation will be as follows: p≤.25=weak correlation, p=.26-.49=low correlation, p=.50-.69=moderate correlation, p≥.70=high correlation.

Specific Aim 2: We will use receiver operating characteristic (ROC) curves to determine the minimal speed and cadence that corresponds to an oxygen consumption value of 10.5 mL/kg/min (i.e. 3.0 METs), as this has been identified by the World Health Organization as 'moderate intensity' activity.[10]

Specific Aims 3 and 6-10: We will use a MANOVA/MANCOVA to evaluate between-group differences with follow-up ANOVAs/ANCOVAs as appropriate (p≤0.05).

Specific Aims 4/5: Regression models will be used to explore relationships between energy expenditure (or average daily step counts) and each of the modifiable factors of interest, while controlling for relevant non-modifiable covariates, e.g. age, residual limb length.

Reported

Dissemination of results will occur through conference presentations and manuscript publications in peer-reviewed journals.

11. **CONFIDENTIALITY**

Will participants be audiotaped, photographed or videotaped during this study? No

How will subject identity be protected?

The risk of breaching subject confidentiality will be minimized by identifying all participants by code numbers and by securing all data in locked files accessible only to research personnel. Neither the participant's name or nor any identifying information will be used in any publication or presentation resulting from this study.

Is there a Certificate of Confidentiality in place for this project? (If so, please provide a copy). No

12. **CONFLICT OF INTEREST**
(For information on disclosure reporting see: http://www.udel.edu/research/preparing/conflict.html)

Do you have a current conflict of interest disclosure form on file through UD Web forms?

Yes

Does this project involve a potential conflict of interest*? No

*** As defined in the University of Delaware's Policies and Procedures ,a potential conflict of interest (COI) occurs when there is a divergence between an individual's private interests and his or her professional obligations, such that an independent observer might reasonably question whether the individual's professional judgment, commitment, actions, or decisions could be influenced by considerations of personal gain, financial or otherwise.**

If yes, please describe the nature of the interest: not applicable

13. **CONSENT and ASSENT**

X Consent forms will be used and are attached for review (see Consent Template under Forms and Templates in IRBNet)

____ Additionally, child assent forms will be used and are attached.
____ Waiver of Documentation of Consent (attach a consent script/information sheet with the signature block removed).
____ Waiver of Consent (Justify request for waiver)

14. **Other IRB Approval**
Has this protocol been submitted to any other IRBs? No

If so, please list along with protocol title, number, and expiration date. Not Applicable

15. **Supporting Documentation**
Please list all additional documents uploaded to IRBNet in support of this application.

- Informed Consent Form – clean copy and track changes
- Data Collection Form – On-site Evaluation (including updated Request for Participant Incentive form)
- Continuing Review Form
- Previously Approved Documents:
    - HIPAA Authorization Form
    - Advertisement
        - Recruitment Flier with Pull Tabs_Controls
        - Recruitment Flier with Pull Tabs_Amputees
        - Recruitment Print Advertisement
        - Consent to Contact Form
    - Other: Screening
        - Verbal Script for Recruitment
        - Telephone Demographics
        - Telephone Screen
    - Mailing Packet Questionnaires
        - Face Sheet
        - Demographics Sheet
        - Medical History Checklist
        - Medication Sheet
        - Activities Specific Balance Confidence Scale
        - Patient-Reported Outcomes Measurement Information System (PROMIS-29)
        - International Physical Activity Questionnaire (IPAQ)
        - Incidental and Planned Exercise Questionnaire-past week
        - Houghton Scale of Prosthetic Use
        - Directions to UDPT Clinic
    - Other: Participant Handouts
        - BP Screening
        - Physical Performance Testing_Controls
        - Physical Performance Testing_Amputees

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