Major Extremity Trauma Research Consortium (METRC):

Patient Response to an Integrated Orthotic and Rehabilitation Initiative for Traumatic Injuries
The PRIORITI-MTF Study

Sponsored by: DOD TATRC

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Version 8

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This template is adapted from the ICH guidance document E6 (Good Clinical Practices), Section 6.

Confidentiality Statement

Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

The Lead Principal Investigator (Protocol Chair) should sign Signature Page 1. A copy of this Signature Page 1 should be filed with the holder of the Regulatory documents and a copy should be maintained at the site.

Principal Investigator: _____

Print/Type

Signed: _____ Date: _____

Name/Title

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List of General Abbreviations/Terminology

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CIB	Clinical Investigator's Brochure
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRO	Contract Research Organization
DCC	Data Coordinating Center
DSMB	Data and Safety Monitoring Board
DSMC	Data and Safety Monitoring Committee
FDA	Food and Drug Administration
FWA	Federal-Wide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDE	Investigational Device Exemption
IEC	Independent or Institutional Ethics Committee
IDEO	Intrepid Dynamic Exoskeletal Orthosis
IND	Investigational New Drug
IRB	Institutional Review Board
ISM	Independent Safety Monitor
MedDRA ©	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
N	Number (typically refers to participants)
NDA	New Drug Application
OHRP	Office for Human Research Protections
OHSR	Office for Human Subjects Research
PHI	Protected Health Information
PI	Principal Investigator
PK	Pharmacokinetics
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
WHO	World Health Organization

List of METRC Abbreviations/Terminology

AFIRM	The Armed Forces institute of Regenerative Medicine
AI	Associate Investigators (Site)
CDMRP	Congressionally Directed Medical Research Program
CCCS	Civilian Core Clinical Sites
CPO	Certified Prosthetist/Orthotist
DOD	Department of Defense
DOD CRMRP	DOD Clinical and Rehabilitative Medicine Program
DOD HRPO	DOD Human Research Subject Protection Office.
DOD PRORP	Department of Defense Peer Reviewed Orthopaedic Research Program
Master Consent Form	Template consent form designed for study by the MCC
Master IRB application	Template IRB application designed for study by the MCC
MCC	METRC Coordinating Center of the Consortium
MCC Study Manager	Principal site contact for Research Coordinators at sites
MTF Core Clinical Sites	Military Treatment Facilities Core Clinical
NMCSD	Naval Medical Center San Diego
O&P Tech	Orthotics and Prosthetics Technician
OETRP	Orthopaedic Extremity Trauma Research Program
PPM	Policy and Procedure Memorandum
SCC	Satellite Clinical Site
RC	Site Research Coordinator
RS	Site Research Staff
Study Number	Protocol identification number
Study Principal Investigator	Lead Investigator on a protocol
Study Protocol Committee	Protocol development
REDCap	Research Electronic Data Capture System
USAMRMC	United States Army Medical Research and Material Command
WRNNMC	Walter Reed National Naval Medical Center

PROTOCOL SUMMARY

Title: Patient Response to an Integrated Orthotic and Rehabilitation Initiative for Traumatic Injuries. The PRIORITI-MTF Study

Sponsor: DOD PRORP

Type of study: Before-after study design; participants serve as their own controls

Objectives: The primary objective of this study is to examine the benefits (and cost-benefits) of an integrated orthotic and rehabilitation program that incorporates the Intrepid Dynamic Exoskeletal Orthosis (IDEO) and the Return to Run (RTR) physical therapy regimen, but designed for scalability in the broader military environment (i.e. beyond San Antonio Military Medical Center where the program was developed).

Participants will be evaluated at baseline (T0), immediately following 4 weeks of physical therapy with the IDEO (T2), at 6 months following completion of all physical therapy (T3) and at 12 months following completion of all physical therapy (T4). **See Figure 1.**

Specific Aim #1: To assess immediate improvements in functional performance following completion of the PRIORITI program. Functional performance will be measured using well-validated assessments of speed, agility, power, and postural stability. Hypotheses to be tested include:

a. *Compared to baseline (T0), functional performance will be significantly better immediately following completion of the PRIORITI program (T8)*

Specific Aim #2: To assess long-term improvements in both functional performance and patient reported outcomes 1 year after completion of the PRIORITI program. Principal hypotheses to be tested include:

a. *Compared to baseline (T0), functional performance will be significantly better at one year following completion of the PRIORITI program (T4)*
b. *Compared to baseline (T0) patient reported outcomes will be significantly better at one year following completion of the PRIORITI program (T4)*

Specific Aim #3: To document patterns of device use, use of ambulatory aids, shoe wear and patient reported satisfaction associated with the IDEO. Participants will be asked about their satisfaction with comfort, cosmesis, ease of use, and durability. As this is primarily a descriptive analysis, no hypotheses will be tested.

Specific Aim #4: To assess the economic impact of the PRIORITI program by (i) measuring one-year costs associated with participation in PRIORITI and compare these costs to those projected under standard of care; and (ii) estimating lifetime cost-effectiveness of the PRIORITI program relative to standard of care. As this is primarily a descriptive analysis, no hypotheses will be tested.

Study design: The effectiveness of the PRIORITI program will be evaluated using a before-after

study design where participants serve as their own controls.

Study duration: 3 years (6 month planning and training, 10 month accrual, 12 month final follow-up, 8 month analysis and writing).

Sample size: 90 participants will be consented to participate in this study.

Number of study sites: 3 Military Treatment Facilities (MTF's).

Inclusion criteria

1. Ages 18-60
2. Currently one or more years out from a traumatic unilateral lower extremity injury at or below the knee
3. Healed fractures and able to fully weight bear
4. Evidence of either:
    a. Weakness of ankle dorsiflexors and /or plantarflexors resulting from leg injury (defined as less than 4 out of 5 on manual muscle test)
    b. Limited ankle dorsiflexion (< 10 degrees) and /or limited ankle plantarflexion (< 20 degrees) resulting from leg injury
    c. Mechanical pain with loading to hindfoot/midfoot (>= 50 mm on a 0-100 mm visual analogue scale assessing average daily pain)
    d. Ankle or Hindfoot fusion or candidate for ankle or hindfoot fusion
    e. Candidate for amputation secondary to ankle/foot impairment

Exclusion criteria

1. Ankle plantarflexion or dorsiflexion weakness as a result of spinal cord injury or central nervous system pathology.
2. Non-ambulatory
3. Surgery on study limb anticipated in next 6 months
4. Medical or psychological conditions that would preclude functional testing (ex. severe traumatic brain injury, stroke, renal failure, heart disease, severe anemia)
5. Neurologic, musculoskeletal or other conditions affecting contralateral extremity preventing the study of a healthy control limb
6. Unable or unwilling to participate in two 4-week PT programs
7. Pregnancy
8. Non-English speaking

Outcome measures

Physical impairment will be determined using objective performance measures of agility (4 step square test and Illinois Agility Test), strength and power (sit to stand test and timed stair ascent), speed (self selected walking speed and 40 yard shuttle run), and postural stability (single leg stance).

Levels of participation will be measured using self reported measures of return to usual major activity (work, active duty, school, home management) and the Paffenbarger Activity Scale (PPAQ) that measures participation in light, moderate and vigorous recreational or sports activities.

Patient reported function and health related quality of life as measured using the total and dimension specific sub scales of the Short Musculoskeletal Functional Assessment (SMFA).

Statistical analysis: We are interested in assessing immediate and long-term improvements in functional performance and self reported outcomes. One-sided paired t-tests will be used to test for improvements in outcomes, comparing baseline data to later outcomes. Differences in means between follow up and baseline will be reported along with 95% confidence intervals.

Analysis of costs and benefits of PRIORITI will include an analysis of costs and outcomes observed over a 12-month period as well as cost-effectiveness projected over the patient lifetime.

Safety monitoring: The Medical Monitor is responsible for monitoring serious adverse events (SAEs) as the study progresses to ensure patient safety. The Medical Monitor may convene a meeting of the DSMB to evaluate any SAEs that he/she determines require immediate attention.

Data Safety and Monitoring Board (DSMB): The DSMB is an independent body responsible for evaluating recruitment, safety and outcome data. The DSMB has the authority to stop the study based on its findings.

1. KEY ROLES

Protocol Committee- Responsible for developing a detailed study protocol, provides oversight on study progress and acts to correct deficiencies in the conduct of the study. This committee also drafts the main publications related to the study.

Steering Committee- Steering Committee is the decision making body of the Consortium and makes decisions regarding study design issues, study procedures, allocation of study resources and priorities for meeting competing demands of the Consortium and individual studies. The Steering Committee is composed of Site Investigators from each core METRC clinical center, the Department of Defense Program Officer for METRC, the orthopaedic consultants from the Army, Navy and Air Force, regional representatives of Satellite Clinical Centers, and the Director, Deputy Director, Principal Biostatistician and Principal Economist of the Coordinating Center. The Steering Committee is responsible for approving the protocol.

METRC Coordinating Center- Responsible for maintaining all study documentation, developing and maintaining the master IRB application and consent, circulating any changes to study documents including protocols, case report forms, and IRB materials to each participating center, providing daily oversight and management of study implementation, providing payment to sites for patients enrolled, performing site monitoring, data quality control and analysis of study results.

Core Clinical Sites- Responsible for the conduct of clinical studies including patient enrollment, performing study procedures, data collection and conducting study follow-up visits.

Publications Committee- Responsible for reviewing manuscripts prior to journal submission and reviewing presentations prior to presentation; for mediating and settling disputes and conflicts among study investigators over publication or presentation priorities, authorship, and any other issues related to publications or presentations; for preparing and maintaining a list of concepts for publications and preparing and maintaining a list of approved METRC publications, which shows the status of each manuscript from initiation through publication.

DSMB- Independent Data and Safety Monitoring Board (DSMB) appointed by DOD, responsible for monitoring the accumulated interim data as the trial progresses to ensure patient safety and to review efficacy, evaluate recruitment, and assess overall data quality.

Medical Monitor- Responsible for providing medical guidance and overseeing patient safety for the study. The MM participates in determining the course of action necessary to meet safety goals and objectives. This is achieved through the review of safety reports; resolving safety issues; and interacting with Principal Investigators.

2. BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

High-energy open fractures, blast, gunshot wound and crush injuries to the distal tibia, ankle, hind foot and midfoot are common challenges to military and civilian trauma surgeons [1-20]. Management of these injuries is complicated by soft tissue injury, ectopic bone, contamination, and neurovascular injuries. Surgical advances have increased capabilities for limb salvage [11-15]. But while prosthetic advances and amputee rehabilitation have facilitated high level function following amputation [16], similar advances in orthotics and rehabilitation for limb salvage patients have been nearly nonexistent. Orthotic options for limb salvage patients have mostly been limited to plastic posterior leaf spring ankle foot orthosis (AFOs). Many limb salvage patients have been unable to achieve their desired functional goals due to volumetric muscle loss [17], ectopic bone, chronic pain and nerve injury [8,13]. In the current military conflict, complications and the inability to achieve the desired level of activity have contributed to high rates of late amputation [18-20].

Current Orthotic Options. Ankle foot orthoses are frequently prescribed for patients with ankle dorsiflexion and plantarflexion weakness due to a variety of etiologies from cerebral palsy in children to trauma and stroke in adults. Numerous types of AFOs exist for different clinical scenarios, each with specific clinical goals for their use. In particular, AFOs are used to counteract both ankle plantarflexion and dorsiflexion weakness by providing support to the ankle joint to prevent excessive activation of the opposing muscle groups (i.e. to counteract large plantarflexion moment in dorsiflexion weakness, and large dorsiflexion moment with plantarflexion weakness). Patients with deficiencies in both of these muscle groups have significant challenges with normal gait, as they are unable to create the large torques and powers needed to overcome these limitations without assistance. Conventional rigid AFOs typically consist of a hard plastic mold extending from the metatarsal heads to the proximal leg. These place the ankle in a neutral position and help to prevent excessive plantarflexion during swing phase that may lead to a "steppage gait," and ensure that the heel contacts the ground at initial strike (first rocker). These AFOs do not provide any assistance with plantarflexion, and cannot contribute to push-off at terminal stance (third rocker) [34-37].

In an effort to provide more plantarflexion power, the "energy-storing AFO" was designed. The design typically involves a carbon fiber material at the posterior aspect of the AFO. Biomechanical data suggests that deformation of the carbon fiber spring which occurs during ankle dorsiflexion in stance (second rocker) is returned during the third rocker allowing for more powerful plantarflexion during step-off. The hope is these devices will allow patients with both plantarflexion and dorsiflexion weakness to have more normal ankle biomechanics and increased ankle power. This, in turn, may lead to increased gait velocity, decreased work of ambulation, and may allow the patient adequate power to run [34-37]. Energy-storing carbon fiber orthoses have been shown to improve abnormal gait patterns, temporal-spatial parameters, increase stride length, ankle power and range of motion in small series of patients [38-41]. However, these studies largely address pediatric patients with cerebral palsy, myelomeningocele or other motor disorders, or adults with hemiplegia. No study to date has investigated the use of energy-storing orthoses in a traumatic limb salvage population.

The Intrepid Dynamic Exoskeletal Orthosis (IDEO) and Return to Run (RTR) Clinical Pathway. The Intrepid Dynamic Exoskeletal Orthosis (IDEO) (**Figure 1**) is a custom, energy-storing carbon fiber orthosis specifically developed at the Center for the Intrepid, San Antonio Military Medical Center (SAMMC) for trauma patients undergoing limb salvage. The IDEO device is an FDA exempt device under 21 CFR 890.3475 and 21 CFR 890.3410. It incorporates a posteriorly mounted carbon fiber strut with a proximal ground reaction cuff and distal supramalleolar AFO. The proximal ground reaction cuff is a circumferential support fashioned in the style of a patellar tendon bearing prosthetic located at the proximal leg, with a posterior attachment to the proximal end of the carbon fiber strut. The distal supramalleolar AFO spans from the posterior attachment to the distal end of the carbon fiber strut, around the ankle joint and under to foot to the toes. A cushioned heel allows for shock absorption during the loading response. The laminated carbon fiber foot plate, which is inspired by prosthetic running feet, is rigid resulting in deformation primarily through the posteriorly positioned carbon fiber strut. This maximizes strut dynamics and power. The plantarflexed position of the footplate combined with a gradual roller shape allows for increased deflection and energy storage as the tibia progresses forward from mid to terminal stance. This also allows for forefoot loading during agility and running activities. The modular design allows for alignment adjustment, the ability to change strut stiffness based on individual patient strength gains, and facilitates donning and doffing to accommodate volumetric muscle changes from strength gains or edema. The IDEO will be labeled with the following information for use in this study: "***CAUTION--Investigational device. Limited by Federal law to investigational use***."

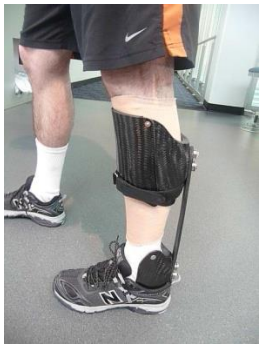


Figure 1: The IDEO

To maximize an individual's potential success in utilizing the IDEO, a high intensity, sports medicine based approach to rehabilitation was developed in collaboration with the departments of orthopaedics, physical therapy and orthotics/prosthetics at the Center for the Intrepid and the San Antonio Military Medical Center. The multidisciplinary Return to Run (RTR) clinical pathway focuses on strength, agility and speed with the goal of enabling patients to return to running, sports and military deployment [21, 23]. Running was chosen as a surrogate for the return to high level function based on the successes of amputation rehabilitation programs [42]. Also, working alongside similar patients who have been fitted with an IDEO provides a built-in support group and helps build self efficacy, which is one of the most important predictors of good outcomes and return to usual activity. The early success of this clinical pathway showed 80% return to running [23]. In addition to success in high level rehabilitation goals, the RTR Clinical Pathway has returned wounded warriors to duty to include deployment [21, 43-44].

Preliminary Studies to Support the Efficacy of the IDEO and RTR Clinical Pathway. In a small study of 18 subjects with unilateral dorsiflexion and/or plantarflexion weakness, the functional performance of the IDEO was compared against two commercially available orhthoses and no orthosis. All participants in this study also completed physical therapy component of the Return to Run Clinical Pathway. Performance wearing the IDEO was compared to that wearing the Allard BlueRocker™ (BR), a rigid plastic posterior leaf spring (PLS), and no brace (NONE) [22]. Subjects were evaluated on six functional tests wearing the IDEO, BR, PLS, and NONE. Brace order was randomized and 5 trials were completed for each measure. Performance was

significantly better in the IDEO on all functional measures compared to all other bracing conditions ($p < 0.004$), with the exception of the sit-to-stand five times, in which there was only a significant improvement against the BR ($p = 0.014$). The forty yard dash improved by 37% over the PLS and NONE, and by 28% over the BR. The BR demonstrated a significant improvement in the forty yard dash compared to NONE ($p = 0.033$), and self-selected walking velocity on level terrain over NONE and PLS ($p < 0.028$), but no significant difference was found between the PLS, BR and NONE in any other functional measure. This study did not, however, evaluate the impact on patient reported outcomes of the improvements in functional performance [43].

2.2 Rationale

The development of a new custom energy-storing ankle foot orthosis (AFO), the Intrepid Dynamic Exoskeletal Orthosis (IDEO), integrated with the RTR Clinical Pathway designed to optimize the patient's adaptation to the IDEO, may significantly improve limb salvage outcomes, reduce the number of delayed amputations, and provide both service members and civilians who undergo limb salvage a higher quality of life [21-24]. While some initial studies point to the benefits of the IDEO, these studies were performed using a small number of patients treated at one military treatment facility (where the IDEO was developed and refined), using measures of functional performance assessed in a controlled environment [22]. Data are needed to replicate the positive results of this study at other military treatment facilities and provide evidence that improvements in performance translate into longer term improvements in functional outcomes and quality of life.

3. STUDY OBJECTIVES

3.1 Primary Objective

To assess immediate and long-term improvements in functional performance and self reported outcomes in patients who are currently one or more years out from a traumatic unilateral lower extremity injury at or below the knee and have chronic muscle weakness and/or limited range of motion at the ankle that translates into functional deficits that interfere with daily activities and overall quality of life.

3.2 Secondary Objectives

To document patterns of device use, use of ambulatory aids, shoe wear and patient reported satisfaction associated with the IDEO. Participants will be asked about their satisfaction with comfort, cosmesis, ease of use, and durability.

To assess the economic impact of the PRIORITI program by (i) measuring one-year costs associated with participation in PRIORITI and compare these costs to those projected under standard of care; and (ii) estimating lifetime cost-effectiveness of the PRIORITI program relative to standard of care.

3.3 Exploratory Objectives

N/A

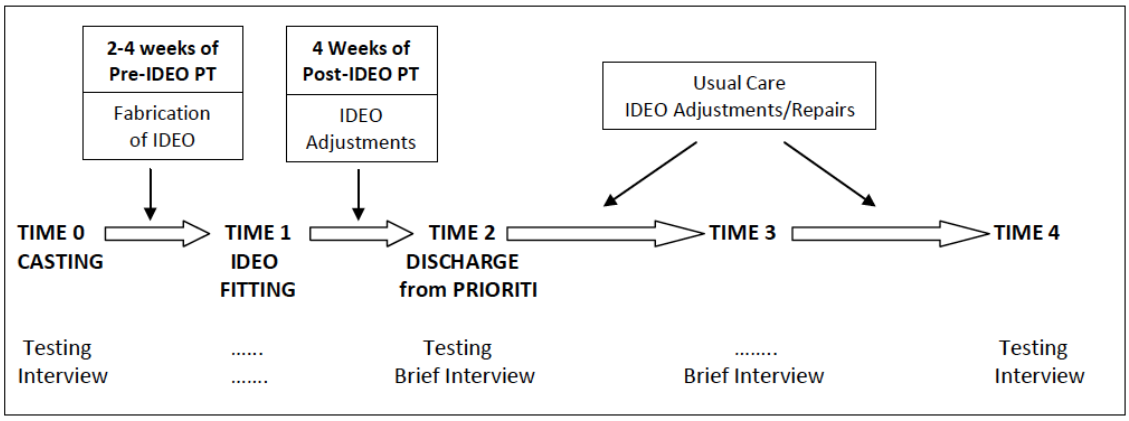
4. STUDY OVERVIEW

The study is a clinical investigation (study) to evaluate the effectiveness of the IDEO, an investigational FDA-regulated medical device. The effectiveness of the PRIORITI program will be evaluated using a before-after study design where participants serve as their own controls. A total of 85 participants at military treatment facilities will be identified at least 1 or more years after their injury. To ensure we are enrolling a 'stable' population, we will exclude individuals whose fractures and soft tissues injuries are not healed at the time of screening or for whom additional surgery is planned within the next six months.

The study will be conducted by the Major Extremity Trauma Research Consortium (METRC) (www.metrc.org). Specifically, participants will be recruited, consented and evaluated at 3 of METRC's core military sites.

The study procedures are summarized in the **Figure below.**

Figure 1: Overview of Study Procedures



At the time of enrollment into the study (T0), all participants (those who have screened eligible and have consented) will be asked to complete a battery of performance tests to measure their baseline assessments of strength, agility, speed and postural stability. They will also complete several standardized assessments of self-reported functional activity, participation in major usual activity and sports and leisure activities, presence of pain, and overall well being. At this time, basic information about the participants, their injury and their use of health and rehabilitation services in the previous year will be collected. After completing these baseline assessments, the Study Site Certified Prosthetist/Orthotist (CPO) will take a cast of the leg and other pertinent measures that are needed for fabrication of the IDEO. The CPO will then fabricate the IDEO brace locally. The final fabricated device given to each subject will be labeled with the following information: "***CAUTION--Investigational device. Limited by Federal law to investigational use***."

During the following 2-4 weeks participants will engage in a home physical therapy (PT) program as directed by the study team. The length of the home physical therapy program is dependant on the time required to fabricate the IDEO™.The focus of the Pre-IDEO PT is conditioning and building self-efficacy. It will build on the principles of the Return to Run Clinical Pathway developed at the CFI.

Following 2-4 weeks of home PT (T1), the participant will be fitted with the IDEO and engage in four weeks of Post-IDEO PT at the study center. During these 4 weeks, adjustments to the brace will be made and the participants will learn how to optimize the use of the brace.

At the end of the four weeks of post-IDEO PT (T2), performance testing will be repeated and overall satisfaction with the device assessed. The purpose of these assessments is to measure any immediate gains in function. Participants will then be formally 'discharged' from the PRIORITI program. They will be given the number of the Study Site Orthotist to call if any concerns arise with the IDEO and its fit. The costs associated with all visits to the orthotist during the 12 month follow-up period will be covered by the study.

At 6 months following the completion of the PRIORITI program (T3), participants will be contacted by the Study Coordinator and asked to participate in a brief interview by phone. The main purpose of this phone call is to keep participants engaged in the study and motivate them to come back to the hospital for the final visit at 12 months. We will also use this opportunity to ask them questions about their functioning, satisfaction with the brace and use of services (overall and specific to the IDEO). This interview will last about 15 minutes. During the call the he coordinator will remind the participant of the 12 month follow up visit. If the participant is living outside of the research site area, the coordinator will inform the participant that travel expenses can be covered for the 12 month follow up visit. (See appendix K).

At 12 months following the completion of the PRIORITI program (T4), participants will be asked to return to the Study Center to repeat the performance tests and self reported measures of outcome and satisfaction with the IDEO. Additional questions regarding use of services (overall and specific to the IDEO) will also be asked.

5. STUDY POPULATION

5.1 Description of the Study Population

A total of 85 participants will be enrolled from 3 METRC Military Treatment Facilities over a 10 month period.

Consenting procedures are described in detail in Sections 8 and 13 of this protocol.

5.1.1 Participant Inclusion Criteria

1. Ages 18-60
2. Currently one or more years out from a traumatic unilateral lower extremity injury at or below the knee

3. Healed fractures and able to fully weight bear
4. Evidence of either:
    a. Weakness of ankle dorsiflexors and /or plantarflexors resulting from leg injury (defined as less than 4 out of 5 on manual muscle test)
    b. Limited ankle dorsiflexion (< 10 degrees) and /or limited ankle plantarflexion (< 20 degrees) resulting from leg injury
    c. Mechanical pain with loading to hindfoot/midfoot (>= 50 mm on a 0-100 mm visual analogue scale assessing average daily pain)
    d. Ankle or Hindfoot fusion or candidate for ankle or hindfoot fusion
    e. Candidate for amputation secondary to ankle/foot impairment

5.1.2 Participant Exclusion criteria
Patients who satisfy any of the following exclusion criteria will be ineligible for enrollment in the study:

1. Ankle plantarflexion or dorsiflexion weakness as a result of spinal cord injury or central nervous system pathology.
2. Non-ambulatory
3. Surgery on study limb anticipated in next 6 months
4. Medical or psychological conditions that would preclude functional testing (ex. severe traumatic brain injury, stroke, renal failure, heart disease, severe anemia)
5. Neurologic, musculoskeletal or other conditions affecting contralateral extremity preventing the study of a healthy control limb
6. Unable or unwilling to participate in two 4-week PT programs
7. Pregnancy
8. Non-English speaking

5.1.3 Co-Enrollment Guidelines
We do not anticipate this patient population will be eligible for other METRC studies.

5.2 Strategies for Recruitment and Screening

Eligible study participants will be identified in several ways as outlined below.

The study center will reach out to orthopaedic surgeons, physical medicine and rehabilitation physicians and physical therapists practicing in the military and veterans community to educate them about the study and ask for referrals of patients they believe may meet the inclusion and exclusion criteria.

The participating study centers will query their orthopaedic registries and identify patients they treated one or more years ago for a severe traumatic lower extremity injury. These individuals will be sent a letter and brochure (explaining the study, its risks and requirements) from their treating physician or the director of orthopaedics if their treating physician is no longer practicing at the facility, and encouraged to contact the center if they think they meet the study criteria (See Appendix H for draft).

We will mount a direct advertising campaign to include local radio and newspaper advertisement, targeting appropriate media outlets frequented by service members and veterans. These advertisements may be produced locally or by the METRC Coordinating Center to maximize our target audience. We will also launch a social media campaign, using the advertisement attached as Appendix J. This advertisement directs potential participants to the PRIORITI website where they are able to access additional information and use our eligibility application. www.prioriti-mtf.org

- LinkedIn
  There are several groups we would like to utilize on LinkedIn for the purposes of posting our advertisement. The only contact information on the ad is the PRIORITI website. We do not intend to facilitate forum discussions, rather interested participants will directed to the PRIORITI website. The groups we intend to target are the following:
  - US Military Veterans Network
  - Wounded Warrior Project
  - Society of Orthotics and Prostetics
  - Disabled American Veterans
  - Stryker, Inc.
  - Hanger, Inc.
  - Orthopaedic Trauma Association
  - Society for Orthotics and Prosthetics
  - The Trauma Network
  - The Lower Extremity Review
  - US Department of Veterans Affairs

- Twitter
  We will use a Twitter account to tweet study inclusion information to selected groups and members. We will contact respected members of those groups (Surgeons, Military personnel etc) and request that they retweet our invitation to be involved in the study. Tweets will contain a unique URL directing participants to the PRIORITI Website.

- Magazine Advertisements
  We plan to purchase a ¼ to ½ page advertisement (Appendix J) that will be printed in various Veterans magazines. Three magazines we plan to target are:

  - Disabled American Veterans
  - American Veteran Magazine (AMVETS)
  - The Journal

- Blogs

There are blogs we would like to utilize for the purpose of posting our advertisement. The only contact information on the ad is the PRIORITI website. We do not

intend to facilitate forum discussions, rather interested participants will directed to the PRIORITI website. The groups we intend to target are the following:

  - http://americanveteranmagazine.blogspot.com/
  - http://www.blogs.va.gov/VAntage/
  - http://warriorcare.dodlive.mil/

- YouTube
  We have an approved recruitment video that is currently posted on the PRIORITI Website. We would like to post the video on YouTube. Prior to posting we would modify the video such that the introduction specifies that interested parties should visit the PRIORITI website for more information and confirmation of eligibility.

- Local Radio Advertisements
  We will utilize the radio script to create a radio advertisement. Both the MCC and local sites will be permitted to run this advertisement on radio stations to broaden the scope of our recruitment efforts. (Appendix G)

- Local News Paper Advertisement
  The MCC and local sites will place the approved advertisement (Appendix J) in local newspapers.

- Facebook
  We will initiate an IDEO brace Facebook page. We will use the IDEO logo as the profile photo and a picture of the brace on a leg as the background photo. The page will use approved advertisement verbiage to provide potential participants with information about the study and brace. Interested participants will be directed to www.PRIORITI-MFT.org. We will adjust the privacy settings such that any "wall posts" will require approval by the page editor (a member of the MCC staff).

To assist in recruitment, a printed brochure and a video are being produced that describe the IDEO and PRIORITI program, the goals of the study, who is potentially eligible for the study and what would be expected of individuals who agree to participate in the study. The recruitment materials will be produced in collaboration with communications experts as well as 1-2 consumers who meet the general inclusion criteria for the study. All recruitment materials will be made available on a website, www.prioriti-mtf.org. This website will also be accessible through the METRC website, www.METRC.org. (A draft of the video script is included in J).

The goal is to develop an effective but efficient process of finding potentially eligible individuals for the study. Individuals who learn about the study through any of the methods described above will be encouraged to contact the local study center *if* they meet the following criteria:

- ✓ Is between the ages of 18 and 60 and able to walk (with or without an assistive device)

- ✓ Had a traumatic injury to their leg (at or below the knee) one or more years ago for which they were initially hospitalized overnight in a hospital
- ✓ Can answer yes to one or more of the following questions:
  - ○ Are you limited in what or how much you are able to do at home, at work or at school because of your leg injury?
  - ○ Are you limited in the types or frequency of sports and recreational activities you would like to do because of your leg injury?
  - ○ Are you dissatisfied with the recovery you have made from your leg injury?

6. STUDY PROCEDURES

6.1 Screening and Enrollment

6.1.1 Screening for Eligibility

As shown in the Figure 2, potential participants in this study will contact the research team at each MTF through physician or self-referral. All referrals will be asked to talk to the Research Coordinator at the local study site. Potential participants can self-refer through the website, www.prioriti-mtf.org. A screening CRF will be completed on every potentially eligible participant and entered into REDCap, the METRC electronic data capture system in order to document screen failures.

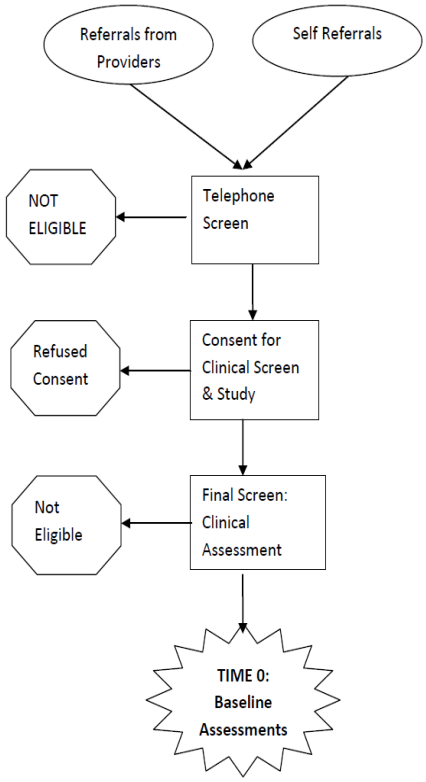


Figure 2

At the time of initial screening, the Research Coordinator will describe the study and if the patient is still interested, will obtain oral consent to conduct a brief telephone screen. The interview will consist of the following:

- Questions about the injury and its initial treatment to confirm the individual is 1 or more years out from a traumatic injury of the lower extremity (at or below the knee) (to include: cause of the injury, when it occurred, where the person was hospitalized and for how long and a description of the injury);
- The Short Form Musculoskeletal Function Assessment (SMFA) to determine whether the individual is impaired or bothered by their level of function due to their leg injury.

Individuals meeting the initial screening criteria will be mailed a consent form and will receive a follow up phone call within 5 business days. If at that time the patient decides to participate, the Research Coordinator will schedule an appointment to come to the study center for testing and final screening to confirm that the patient meets the final inclusion/exclusion criteria for the

study. The final (in person) screen will consist of a clinical assessment, medical history, and interview.

6.1.2 Consent and Enrollment

A prototype consent has been prepared for the PRIORITI study and is attached in Appendix D. Individual sites may add material but may not delete material thought to be necessary for informed consent. Clinical sites may reformat and reword information to conform to their local requirements. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. Copies of the signed consent forms will be given to the patient, and this fact will be documented in the patient's record.

Informed consent will take place at the study center before beginning the final in-person screen. The conversation will be initiated by the Research Coordinator and surgeon investigator together. Patients will be provided a pamphlet describing the study, the risks and benefits of participation and what will be expected of them if they choose to participate. After reviewing all components of the informed consent form, the surgeon investigator and the Research Coordinator will answer any questions the patient has about participating in the study. Consent will be obtained in accordance with principles of GCP and ICH guidelines.

Following completion of informed consent, the surgeon investigator will conduct a clinical assessment, medical history, and interview to confirm eligibility. Patients who are ineligible will not continue in the study and will be withdrawn.

All patients must be able to provide informed consent; there will be no consent by Legally Authorized Representatives.

All study materials will be provided in English.

Additionally, after completion of informed consent, the participant information will be entered into REDCap where a study number will be assigned and final eligibility criteria confirmed.

6.1.3 Assessing Capacity to Consent and Consenting a Proxy Respondent
N/A

6.1.4 Informed Consent Process or Assent (for a minor)
N/A

6.2 Baseline Data Collection

Once consented into the study, baseline data regarding participant characteristics, injury characteristics, fracture classification and medical history/co-morbidities will be collected and entered into the REDCap data collection system. An x-ray will be obtained to confirm healing of the fracture and to identify presence of post-traumatic osteoarthritis. This x-ray will be used to confirm suitability of the IDEO for the individual. If, based on the x-ray, a decision is made that

the patient is *not* suitable to receive the intervention, he or she will be withdrawn from the study. Participants who remain eligible will complete a performance assessment and a brief interview.

For patients treated acutely (initially at the time of the injury) in an institution other than the recruiting institution, permission will be sought from the participant to access the medical records pertaining to the initial hospitalization.

The data collected at baseline are described below. These data are summarized in Appendix C.

6.2.1 Baseline Clinical Assessment and Medical History

- Study Injury Characteristics
    - Mechanism, Type, Side of Injury
    - Classification of Fracture (AO/OTA and Gustilo)
    - Presence of other limb and non-limb injuries (ICD-9CM codes)
- Current Limb Status
    - ROM and Strength of study limb
    - Radiographic Evaluation of Healing (from x-ray)
    - Evidence of PTOA (from x-ray)
    - VAS Pain and Use of Narcotics
- Height and Weight
- Co-morbidities
- Smoking History

6.2.2 Performance Assessments

- 4 Square Step Test
- Illinois Agility Test
- Sit to Stand
- Timed Stair Ascent
- Self Selected Walking Speed
- Shuttle Run
- Single Leg Stance

6.2.3 Participant Interview

- Age, gender, race and ethnicity, education, and income (past year)
- Marital status
- Usual major activity status
- If working, what type of work and physical demands of the job; Work Productivity (WPAI)
- Job Motivation
- Multidimensional Scale of Perceived Support (MSPS)
- Health insurance
- Self Efficacy to perform major usual activity
- Short Musculoskeletal Function Assessment (SMFA)
- Veterans Health Survey (VR-12)
- Paffenbarger Activity Scale (PPAQ)

- Brief Pain Inventory (BPI)
- Patient Health Questionnaire Dépression Scale (PHQ-9)
- Post Traumatic Stress (PCL Checklist)
- Shoe Wear and Use of Ambulatory Aids
- Hospitalizations in Past Year
- Use of Orthotic Services in Past Year
- Use of PT/OT Services in Past Year
- Use of Other Services Related to the Injury in Past Year

If, during the course of completing the PHQ-9 or PCL via participant self-report survey or interview, a participant has a PHQ-9 score indicating major depressive disorder (>=20) or has a PCL score indicating clinically significant PTSD (>=30), the participant will be notified and advised to contact his/her physician or to visit the emergency department.

If on the PHQ-9 item #9, the participant reveals that he/she has thoughts of being better off dead or of hurting themselves in any way, more often than "not at all," the coordinator will ask the following questions to the participant:

1	Interviewer:	Let me ask another question, have you thought of hurting yourself in any way?
	Participant:	Yes No *If no: "It is difficult having thoughts like this. You should talk to your doctor about these thoughts, as you may benefit from treatment for depression." Continue with interview.* *If yes: Continue with following questions.*
2	Interviewer:	Does your doctor know about this?
	Participant:	Yes No *If yes: "It is difficult having thoughts like this. You should talk to your doctor about these thoughts, as you may benefit from treatment for depression."* *Continue with interview.* *If no: Continue to following questions.*
3	Interviewer:	Have you talked to another clinician, like a counselor or psychologist, about how you have been feeling lately?
	Participant:	Yes No *If yes: "It is difficult having thoughts like this. You should talk to your doctor about these thoughts, as you may benefit from treatment for depression." Continue with interview.* *If no and if in-person: "I am not a clinician, but we want a clinician on the*

		study to talk with everyone who tells us they have been feeling this way recently. I would like Dr. _____ or Dr. _____ to speak with you today. If you are having thoughts of hurting yourself, the best thing to do is to go to the emergency department or call the National Suicide Prevention Hotline (1-800-273-8255)." *If no and if on phone: "I am not a clinician, but we want a clinician on the study to talk with everyone who tells us they have been feeling this way recently. I would like Dr Stephen Wegener to give you a call today or tomorrow. If you are having thoughts of hurting yourself, the best thing to do is to go to the emergency department or call the National Suicide Prevention Hotline (1-800-273-8255)."*

6.3 Participant Follow up and Data Collection

The follow up visit schedule for this study will be closely related to the timing of brace fitting and PT participation. Follow up will occur immediately following post-IDEO PT (T2), 6 months following completion of all PT (i.e. post PRIORITI) (T3), and 12 Months post PRIORITI (T4). Each visit will have an interval of time surrounding the ideal date for the visit during which the visit may be completed and the data included in the trial database. This interval is approximately 1-2 weeks before or after the ideal date for a visit.

The data collected at follow-up are described below. These data are summarized in Appendix C.

6.3.1 Performance Assessments (at,T2, T4)

- 4 Square Step Test
- Illinois Agility Test
- Sit to Stand
- Timed Stair Ascent
- Self Selected Walking Speed
- Shuttle Run
- Single Leg Stance

6.3.2 Clinical Assessment at T4

- Weight
- ROM and Strength
- VAS Pain and Use of Narcotics

6.3.3 Participant Interviews at T2

- Use and Satisfaction with Brace (OPUS & CFI)
- Shoe wear and ambulatory aids

6.3.4 Participant Interviews at T3

- ALL ITEMS ASKED AT T2 PLUS:

- Short Musculoskeletal Function Assessment (SMFA)
- Veterans Health Survey (VR-12)
- Usual major activity status
- If working: Work Productivity (WPAI)
- Hospitalizations in past 6 months
- Use of Orthotic Services in past 6 months
- Use of PT/OT Services in past 6 months
- Use of other Services in past 6 months

6.3.5 Participant Interviews at T4

- ALL ITEMS ASKED AT T3 PLUS:
- Income (past year)
- Health Insurance (current)
- Self Efficacy
- Multidimensional Scale of Perceived Support (MSPS)
- Activities- Paffenbarger Activity Scale (PPAQ)
- Brief Pain Inventory (BPI)
- Patient Health Questionnaire Dépression Scale (PHQ-9)
- Post Traumatic Stress Disorder using the PCL Checklist

6.3.4 Retention

Every effort will be made to retain participants in the study. The study participants will receive an honorarium in recognition of their time and effort. We will provide them with challenge coin designed specifically for the METRC and (for those not on active duty), a total of $300 to cover the costs of travel to and from the centers for the physical therapy and follow-up assessments and keep in contact with them throughout the one-year follow-up (by mail and phone). This sum will be distributed as follows: $50 at baseline (T0), $75 at T1, $75 at T2 and $100 at T4. We will also keep participants engaged through use of study updates on the METRC webpage and distribution of follow-up reminders and trinkets imprinted with the study logo.

6.3.5 Final Study Visit

Participants will complete the study at month 12. Any ongoing SAE's will be followed to resolution. The study will cover the travel expenses for participants that have moved out of the area so that they can participate in the 12 month follow up visit. Expenses that will be covered include: transportation to and from the study center (airfare, bus fare or mileage reimbursement), lodging expense (up to 1 night, if needed), meal per diem of 50.00 per day (2 day maximum).

6.3.6 Early Termination Visit

Should a participant terminate the study prematurely, if at all possible, all procedures required at the month 12 (T4) visit will be performed at his/her final visit.

6.4 Study Endpoints

	Less Demanding Tests	More Demanding Tests
Agility	4 Square Step Test	Illinois Agility Test
Strength/Power	Sit to Stand (5x)	Timed Stair Ascent (12 steps)
Speed	Self Selected Walking Speed (15 ft)	10 Meter Shuttle Run
Postural Stability	Single Leg Stance	

6.4.1 Primary Endpoints

The primary endpoints are functional performance and self reported functioning as measured suing the Short Form Musculoskeletal Assessment (SMFA) and the Veterans Health Survey (VR-12).

Functional Performance The performance test battery includes a dyad of a "less demanding" test and a "more demanding" test for three of the domains. At the study initiation visit, the treating surgeon will clinically evaluate the participant's health, weight bearing and ambulatory status and will provide written approval in order to proceed with the performance tests. Prior to and during the performance tests, the participant will be reminded that he/she can stop these activities at any point if he/she feels unsafe. Participants in the study will complete the "less demanding" test first and, if the score meets a critical threshold, they will move on to complete the "more demanding" test. This approach will provide information on higher level functioning without risking the safety of those with significant impairment. These dyads are summarized in the table below.

Details of each of these assessments are provided below.

- **The Four Square Step Test (FSST)** is a dynamic test of balance and agility. It requires participants to rapidly change direction while stepping forward, backward, and sideways, over a low obstacle [54]. The test has demonstrated reliability and validity through correlation with existing balance tests and a positive predictive value of 86% [54]. The FSST does not require any special equipment and requires little space, and is timed using a stopwatch. Raters place four canes (or piping) in a cross on the floor (all four canes lay flat on the floor). The participant then steps as fast as possible into each square in a designated sequence (see Figure 3).

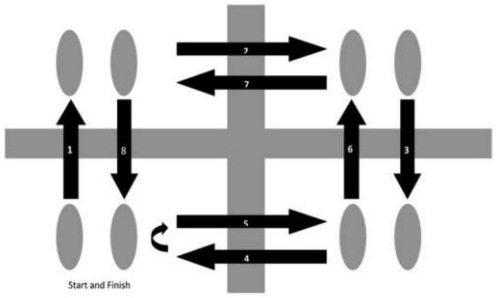


Figure 3: the Four Square Step Test

- **The Illinois Agility Test** [54] is a commonly used test to measure agility by requiring the patient to turn in different directions and at different angles. The test requires the patient to

navigate through a series of cones placed 3.3 meters apart as quickly as possible. It is simple test to administer and requires little equipment. The test is timed using a stopwatch and requires 10 meters of length, 5 meters of width, and 8 cones (or markers of some kind).

- **The 5x Sit to Stand Test (STS5)** [54-61] is a commonly performed to assess lower extremity strength, endurance, and mobility. This test measures time to complete 5 full stands from a sitting position. It is simple, inexpensive, rapid, and reproducible, has demonstrated a highly significant relationship with age and has correlated well with measures of knee flexor and extensor muscle strength [61]. Participants sit in a straight back chair 44.5 cm high and 38 cm deep and are asked to fold their arms across their chests and to stand up from a sitting position once. If they successfully rise, they are asked to stand up and sit down 5 times as quickly as possible. Time to stand is measured using a stopwatch. Raw scores can be transformed into a rate per minute to accurately assess change in those who were unable to perform the test at any point.

- **Timed Stair Ascent**: The timed stair ascent is an objective measure of mobility and power [62] that requires the patient to demonstrate greater strength and range of motion than level ground walking. Patients are asked to climb a flight of stairs at their maximal rate, with or without holding onto the railing. The rater uses a stopwatch to time the patient's ascent up 12 stairs of normal rise and run. The inclusion of this test provides data on higher levels of functional performance because of the level of challenge involved in climbing stairs

- **Self-selected walking velocity over level terrain (SSWV-L)** is a commonly used measure of speed and general physical capacity.[62-64]. Subjects will be asked to walk 30 feet on a level surface, as fast as they can, with or without an assistive device. Use of assistive devices will be recorded, as described above. The time it takes for subjects to complete the task is measured with a stop watch and recorded as feet per second (ft/sec). Use of a stopwatch has been found to have excellent concurrent validity with the gold standard of infrared timing gates, with an inter-rater reliability of 0.99 for tests of walking speed [64]. Four feet per second is considered an appropriate cut-off for impaired speed, since 4.2 ft/sec is an approximate gait velocity for adults, 20-59 years old [63].

- **10 Meter Shuttle Run (40D)**: The 10 meter shuttle run assesses speed. Research staff will measure out a continuous 10 meter stretch that is free of obstacles. This test requires the person to run or walk back and forth between two parallel lines as fast as possible. Patients will start in a standing position and run or walk at their self-selected maximal rate 10 meters and back, for a total of 20 meters. The rater uses a stopwatch to keep time. The Shuttle Run test is easy to administer and requires little equipment and space. Patients are able to run or walk at their own pace, and the test is appropriate for patients at both lower and higher levels of functional ability.

- **Single Leg Stance:** The single leg stance is a measure of postural stability [66]. Participants will be asked to stand with arms crossed and pick one foot off the ground bending the knee to 90 degrees. The rater uses a stopwatch to time how long participants hold this stance up to 60 seconds. This test is done on both legs.

Self -Reported Measures of Function will be assessed at baseline (T0) and at one-year (T4).

Overall Function and Well Being will be measured using two instruments. The Short Musculoskeletal Function Assessment (SMFA) will be used to measure overall function and well being [67-68]. The SMFA is a shorter version of the 101-item Musculoskeletal Function Assessment (MFA) questionnaire. The SMFA is a 46-item questionnaire consisting of the dysfunction and bother index. The Dysfunction Index includes 34 items for assessing patient function. Subscores for the following 4 domains can be calculated: Daily Activities; Arm and Hand Function; Mobility and Emotional Status. The Bother Index consists of 12 items designed to detect how much patients are bothered by functional items. The SMFA has been evaluated for reliability, validity and responsiveness in patient populations [67]. This scale has been chosen because it is a short, reliable, patient reported assessment of functional status that has been specifically designed for and validated in patients with musculoskeletal conditions, including acute injury [67-68].

We will also use the Veterans RAND 12 item Health Survey (VR-12) as a generic health status measure from which a VR-6D can be computed for a cost-utility analysis [69-70]. The VR-12 is a multipurpose short-form generic measure of health status. It was developed to be a much shorter, yet valid, alternative to the VR-36 for use in large surveys of general and veteran populations. The 12 items in the VR-12 are a subset of those in the VR-36 and includes 1-2 items from each of eight health concepts: physical functioning, role limitations due to physical health problems, bodily pain, general health, vitality (energy/fatigue), social functioning, role limitations due to emotional problems and mental health (psychological distress and psychological well being).

6.4.2 Secondary Endpoints

Secondary Outcomes include additional self reported measures of participation, pain, depression and post traumatic stress. We will also be the use and satisfaction with the IDEO and related services.

- **Labor Force Participation and Work Productivity** will be assessed using standard questions used in other METRC studies. Participants will be asked what they were doing most of the time during the previous two weeks. If participants are working, the Work Productivity and Activity Impairment (WPAI) questionnaire will be administered. The WPAI measures work time missed and work and activity impairment because of a specified health problem during the past 7 days (for questionnaire: http://www.reillyassociates.net/WPAI_SHP.html) [71]. The validity of the WPAI has been established in a number of diseases [72-73]. In addition, the WPAI has proven a useful tool when measuring the relative difference between treatment groups in clinical trials and in subjects with and without disease.

- **Participation in Sports and Leisure Activities** will be assessed using the Paffenbarger Activity Scale (PAS) [74]. At T0 (baseline) and at T4 (one year post fitting of the IDEO), patients are asked to identify up to 5 activities performed within the past 3 months. The 2000 version of the *Compendium of Physical Activities* [75] will be used to classify each activity according to its intensity level based on the rate of energy expenditure expressed as

metabolic equivalents (METS). Activities will then be classified as light (< 3 METS) moderate (3-6 METS) or vigorous (> 6 METS).

- **Pain** will be measured using the Brief Pain Inventory (BPI**)**. The BPI is a widely used, 15-item measure of pain intensity and interference with daily life [76]. The questionnaire assesses three key pain domains: pain intensity, pain interference, and efficacy of pain treatments or medications. It has been extensively validated in both English and Spanish. Overall study limb as well as knee and ankle specific pain intensity will be measured using the 0-10 visual analogue scale used in the Brief Pain Inventory. Pain intensity will be measured both at rest and during ambulation. The BPI pain intensity domain is compatible with the IMMPACT guidelines for assessing pain in clinical trials and the FDA Guidance for Industry on the use of Patient-Reported Outcome Measures [77]. At each clinical follow up, the treating surgeon will also record the type (grouped as acetaminophen, opioids, GABA analogues (like Neurontin or Lyrica), and NSAIDs (like Ibuprofen or Naproxen), and other) and frequency of pain medication use.

- **Depressive Symptoms** will be assessed using the nine item depression scale of the Patient Health Questionnaire (PHQ-9) [78]. The PHQ-9 is a well validated tool for assisting clinicians in diagnosing depression. There are two components of the PHQ-9: (1) assessing symptoms and functional impairment to make a tentative depression diagnosis, and (2) deriving a severity score. The PHQ-9 is based directly on the diagnostic criteria for major depressive disorder in the Diagnostic and Statistical Manual Fourth Edition (DSM-IV).

- **Post Traumatic Stress (PTSD)** will be measured using the standard PTSD Checklist (PCL), a 17-item measure that elicits responses for each of the DSM-IV disorders that comprise the diagnostic criteria for PTSD (intrusive, avoidant, and arousal symptoms) [79]. The psychometric properties of the PCL have been well established and it is the most widely used measure of PTSD. Both civilian and military versions are available.

- **Use and Satisfaction with the IDEO and Related Services.** At T2 (following completion of the physical therapy program), and at T3 and T4, each patient will complete a brief battery of questions to assess their use and overall satisfaction with the IDEO™ and related services. We will include both the Orthotics and Prosthetics Users' Survey (OPUS) [81-82] and elements of a survey developed at the Center for the Intrepid (designed specifically for comparing the satisfaction of the IDEO with other braces) [22]. The OPUS was developed by Heinemann et al. using well established contemporary measurement technology for instrument development. The OPUS consists of an 11-item measure for satisfaction with *devices* and a 10-item measure for satisfaction with *services*. Items pertaining to device satisfaction include: weight, comfort, pain associated with use, ease of use, cosmesis, durability, fit and effect of the device on clothing (i.e., dimensions). Items used to measure satisfaction with services, include wait time, respect, communication, consumer's input, team approach, and training with the device. Lastly, participants will be asked if they ever considered amputation of their injured limb, if so, why, and if they now favor limb salvage or amputation.

6.4.3 Exploratory Endpoints
N/A

6.4.4 Substudy Endpoints
N/A

7. STUDY TREATMENTS

The PRIORITI intervention consists of two components: (1) custom fitting of the IDEO; and (2) the Return to Run physical therapy program designed specifically for recipients of the IDEO. Each is described below together with specifics regarding the training of Study Site staff to ensure fidelity of the intervention across sites.

All braces will be fabricated by trained Certified Prosthetist/Orthotists (CPOs) at each participating MTF. Training for fabrication of the IDEO is described below. The two participating study MTF sites will each identify 1-2 physical therapy assistants and 1 CPO and 1 O&P tech who will provide the services necessary for measuring, fabricating and fitting the IDEO and providing the PT. Only PTAs and orthotists who have been trained for the study (see below) will be allowed to provide services to PRIORITI participants.

7.1 Fabrication and Fitting of the IDEO. The IDEO design for this study will be the modular version, since it has the advantage of modifying alignment in a simpler manner, adjusting strut stiffness for limitations or gains of individuals, and limiting fabrication responses needed for fissuring or fracturing of components of the device with use. The IDEO is constructed primarily of laminated, reinforced carbon fiber to withstand high impact forces and cyclical loading. The main components of the IDEO are the proximal cuff, strut, and foot plate. These components are described in further detail in Appendix J. The IDEO is a class 1 exempt device. A provisional patent was filed in April, 2011 by Ryan Blanck, CPO in conjunction with the United States Government, as represented by the Secretary of the Army (Application Serial No. 61/518,801).

The team at the Center for the Intrepid (CFI) will train the CPOs from the other two military treatment facilities in IDEO fabrication. Training will consist of a 6-8 week internship working with the San Antonio team to learn the processes of measurement, fabrication, and fitting of the brace. Training materials will be developed through this process and used in subsequent training sessions. Once able to replicate the process, the CPOs will return to WRNNMC and NMCSD to implement the program at their institutions

7.2 Physical Therapy Protocol. As indicated above, participants enrolled in PRIORITI will participate in the Return to Run physical therapy regimen. During Phase 1 (pre-IDEO) participants will engage in a home physical therapy program as prescribed by the study team for 2-4 weeks. During Phase 2 (post-IDEO), participants will receive 3 sessions of PT a week for an additional 4 weeks. Participants will be encouraged to test the IDEO under load in real world

conditions and report their experience to the study team. Each PT session will last for approximately 90 minutes. During phase 2, participants will be encouraged to complete home exercises to complement the therapy they are receiving in the clinic.

To help ensure standardization of the PT protocol across centers, several procedures will be put in place. *First,* the PTAs providing the pre-IDEO and post-IDEO physical therapy must have some documented training in sports medicine and experience working with limb trauma patients. They will be trained in the PT protocol at a 3-day training at the Center for the Intrepid in San Antonio. The 3 days will be devoted to the PT protocol with ample use made of demonstrations and practice sessions. As mentioned above, training videos will be produced and provided to the PTs or PTAs for reference. *Second,* the PTAs will be required to document the therapy provided at each session. This documentation will be reviewed on an ongoing basis by the investigators to assure the fidelity of the intervention. *Third,* the PTAs will participate in bi-weekly video conference calls together with Mr. Owens at which time individual cases will be reviewed and difficulties in providing the PT and keeping patients engaged in the program will be discussed.

8. ASSESSMENT OF SAFETY

The study will monitor and report adverse events to ensure patient safety. Definitions and procedures for reporting adverse events are designed to satisfy 45 CFR Part 46, Subpart A; the "Common Rule", shared by 17 Departments and Agencies as well as 21 CFR 312, the FDA regulation for adverse events. The Common Rule requires written procedures and policies for ensuring reporting of "unanticipated problems" involving risks to participants to IRBs, appropriate institutional officials, and the Department or Agency Head.
The medical monitor (MM) is responsible for providing medical guidance and overseeing patient safety for the study. The MM participates in determining the course of action necessary to meet safety goals and objectives. This is achieved through the review of Serious Adverse Event reports; resolving safety issues; and interacting with Principal Investigators.
Each participating site is responsible for ensuring that all local IRB requirements for reporting adverse events (both internal and external) are met.

8.1 Definitions

8.1.1 Adverse event

Any untoward or unfavorable medical occurrence in a human subject, including abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom or disease temporally associated with the subject's participation in the study, whether or not considered related to the subject's participation.

8.1.2 Unanticipated problem

Any incident, experience, or outcome that meets all of the following criteria:

(1) is unexpected, in terms of nature, severity, or frequency, given the research procedures that are described in the protocol and informed consent document and the characteristics of the patients eligible for the study.

(2) is related or possibly related to treatment/procedures under study; possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the study procedures or treatments.

(3) suggests that the participation in the study may place subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Please note that not all adverse events are unanticipated problems and only some unanticipated problems are in fact adverse events. For instance, if a laptop containing study data is stolen, this is an unanticipated problem but it is not an adverse event since it is not an untoward or unfavorable medical occurrence in a human subject

8.1.3 Serious Adverse Event

A serious adverse event is defined as:

1. Death
2. Unanticipated events related to rigor of participating in the Return to Run PT Program; or events related to IDEO brace fit or wear.
3. Other events that are unexpected AND serious AND related or possibly related to the study

8.2 Methods and Timing for Assessing, Recording, and Analyzing, Managing Safety Parameters

8.2.1 Methods and Timing of Assessment

Adverse events may be discovered during regularly scheduled visits or through unscheduled patient contacts between visits. Adverse events related to study procedures would be assessed during the index hospitalization and at each study visit. They will be recorded on study data forms whether or not they are thought to be associated with the study.

8.2.2 AE/SAE Grading and Relationship Assignment

Adverse event grading: Adverse events will be graded using standard criteria. The study physician will determine relationship of event to the study procedure.

GRADE 1 (Mild) Transient or mild discomfort (< 48 hours); no medical intervention/therapy required

GRADE 2 (Moderate) Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required

GRADE 3 (Severe) Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible

GRADE 4 (Life-threatening) Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable.

Relationship Assignment The relationship of the adverse event to participation in the study will be assessed as either:

Definitely related
Probably related
Possibly related
Unlikely related
Unrelated

8.2.3 Recording and Documentation

Sites will maintain source documents including but not limited to (laboratory and radiology reports, clinical notes and discharge summaries). After review of initial and final reports by the medical monitor, the events may be reclassified at their discretion.

8.2.4. Management of Adverse Events

Adverse Events and Serious Adverse Events will be managed according to protocol guidelines. If specific guidelines do not exist, AEs/SAEs will be managed according to the medical judgment of the treating physician.

8.3 Adverse Event Reporting Procedures

8.3.1 Local Reporting Requirements.

Study sites must always follow and comply with their own local institution's adverse event reporting requirements, which may differ from those adopted by the PRIORITI Study**.** Depending on the local requirements, a site may report events locally and not report those events to the METRC Coordinating Center. Each participating site is responsible for ensuring that all local IRB requirements for reporting adverse events (both internal and external) are met.

8.3.2 SAE and Unanticipated Problem Reporting Requirements

All Serious Adverse Events that are Unexpected AND related or possibly related to the study must be reported to the Medical Monitor and METRC Coordinating Center within 72 hours of being made aware of the event.

In addition, Unanticipated Problems (UPs) that are not adverse events must also be reported to the METRC Coordinating Center within 14 calendar days after the event has been discovered.

SAEs/UPs will be reported to the METRC Coordinating Center by entering the SAE/UP form into REDCAP. REDCap is programmed to automatically send an email to the Coordinating Center for both SAEs and Ups, and to the Medical Monitor in the case of an SAE.

The Medical Monitor for this study is:
Mark Swiontkowski, MD, FACS
Department of Orthopedic Surgery
2450 Riverside Ave., R200
Minneapolis, MN 55454
Telephone: (612) 273-7951
Fax: (612) 273-7959
E-mail: swion001@umn.edu

8.3.3 METRC Coordinating Center Reporting Responsibilities

As appropriate and per METRC policies, the Coordinating Center will send a copy of each report received about an event judged reportable to all clinical sites, with instructions for each to forward the report to their IRB.

Copies of the report will also be sent to the DoD, the Study PI, and to the Medical Monitor. The MCC will maintain a list of such events for reporting and review at Steering Committee meetings.

8.3.4 Department of Defense Reporting Requirements

The following are reporting requirements and responsibilities of the Principal Investigator to the United States Army Medical Research and Materiel Command's (USAMRMC) Office of Research Protections (ORP), Human Research Protection Office (HRPO).

(1) The protocol will be conducted in accordance with the protocol submitted to and approved by the USAMRMC ORP HRPO and will not be initiated until written notification of approval of the research project is issued by the USAMRMC ORP HRPO.

(2) Accurate and complete study records will be maintained and made available to representatives of the U.S. Army Medical Research and Materiel Command as a part of their responsibility to protect human subjects in research. Research records will be stored in a confidential manner so as to protect the confidentiality of subject information.

(3) All unanticipated problems involving risk to subjects or others, serious adverse events related to participation in the study and subject deaths related to participation in the study will be promptly reported by phone (301-619-2165), by email (hsrrb@.amedd.army.mil), or by facsimile (301-619-7803) to the USAMRMC, Office of Research Protections, Human Research Protection Office. A complete written report will follow the initial notification. In addition to the methods above, the complete report will be sent to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-RP, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

(4) Suspensions, clinical holds (voluntary or involuntary), or terminations of this research by the IRB, the institution, the Sponsor, or regulatory agencies will be promptly reported to the USAMRMC ORP HRPO.
(5) Any deviation to the protocol that may have an adverse effect on the safety or rights of the subject or the integrity of the study will be reported to the USAMRMC ORP HRPO as soon as the deviation is identified.
(6) Major modifications to the research protocol and any modifications that could potentially increase risk to subjects will be submitted to the USAMRMC ORP HRPO for approval prior to implementation. All other amendments will be submitted with the continuing review report to the USAMRMC ORP HRPO for acceptance.
(7) A copy of the approved continuing review report and the local IRB approval notification will be submitted to the USAMRMC ORP HRPO as soon as these documents become available. A copy of the approved final study report and local IRB approval notification will be submitted to the USAMRMC ORP HRPO as soon as these documents become available.
(8) The knowledge of any pending compliance inspection/visit by the FDA, OHRP, or other government agency concerning this clinical investigation or research, the issuance of Inspection Reports, FDA Form 483, warning letters or actions taken by any Regulatory Agencies including legal or medical actions and any instances of serious or continuing noncompliance with the regulations or requirements that relate to this clinical investigation or research will be reported immediately to USAMRMC ORP HRPO.

Unanticipated problems involving risk to volunteers or others, serious, unexpected adverse events related to participation in the study and all volunteer deaths related to participation in the study will be promptly reported by phone (301-619-2165), by e-mail (hsrrb@amedd.army.mil), or by facsimile (301-619-7803) to the U.S. Army Medical Research and Materiel Command's Office of Research Protections, Human Research Protections Office. A complete written report will follow the initial notification. In addition to the methods above, the complete report will be sent to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-RPH, 504 Scott Street, Fort Detrick, Maryland 21702-5012

8.4 Reporting Pregnancy

N/A

8.5 Type and Duration of the Follow-up of Participants After Adverse Events

Study patients who experience an SAE will be followed until resolution of the event, and a final report will be submitted to the medical monitor, and the coordinating center.

8.6 Modifications of Study Agent(s)/Intervention(s) for a Participant

N/A

8.7 Halting Rules for the Protocol

N/A

8.8 Stopping Rules for an Individual Participant/Cohort
N/A

8.9 Premature Withdrawal of a Participant

A participant may be withdrawn from the study without consent if the sponsor decides to end the study. Other reasons for removing a participant without consent may include but are not limited to non-adherence with the protocol and/or therapy, and inappropriate behavior towards study personnel.

8.10 Replacement of a Participant Who Discontinues Study Treatment N/A

9. MONITORING

9.1 Site Monitoring Plan

The METRC Coordinating Center will be responsible for site monitoring consistent with ICH/FDA guidelines. Monitoring will include a combination of remote and on-site visits of participating clinical research sites to review the individual subject records, including consent forms, case report forms, supporting data, and medical records (physicians' progress notes, nurses' notes, individuals' hospital charts), to ensure protection of study subjects, compliance with the protocol, and accuracy and completeness of records. The monitors also will inspect sites' regulatory files to ensure that regulatory requirements are being followed.

The site PI will make study documents (e.g., consent forms, case report forms) and pertinent hospital or clinic records readily available for inspection by the local IRB, the site monitors, the DOD, the Office for Human Research Protections (OHRP), or other regulatory authorities for confirmation of the study data.

9.2 Safety Monitoring Plan

9.2.1 Safety Review Plan by the DSMB

A DSMB is not required for this study. A Medical Monitor has been appointed and will review any SAEs, unanticipated problems involving risk to participants or others and all deaths.

10. STATISTICAL CONSIDERATIONS

10.1 Overview and Study Objectives
The primary objective of this study is to assess immediate and long-term improvements in functional performance and self reported outcomes following completion of the PRIORITI program.

Secondary objectives include documenting patterns of device use, use of ambulatory aids, shoe wear and patient reported satisfaction associated with the IDEO, and assessing economic impact of the PRIORITI program.

10.2 Sample Size Considerations

A total of 85 patients will be consented and enrolled by the military core METRC centers (approximately 25-30 from each center); data collected from these participants will be used to test the research hypotheses.

We anticipate a low dropout rate (<5%) because highly motivated individuals will self-select themselves into the program. We will also provide a modest compensation to participants who are not on active duty for their time and travel. For power calculations we assume we will have complete follow-up data on 80 of the 85 participants who enroll. All functional and satisfaction outcomes are continuous. In Specific Aim 1a and Specific Aims 2a and 2b, we plan to test for improvements in outcomes at a specified point in time after enrollment (8 weeks for Specific Aim 1a and 1 year for Specific Aims 2a and 2b) as compared to baseline. One-sided paired t-tests will be used. Differences in means between follow-up and baseline will be reported along with 95% confidence intervals. The proposed sample size yields 80% power to detect an effect size (mean of the difference in outcomes between follow-up and baseline divided by the standard deviation of the difference) of 0.28 (a modest treatment effect). To put this effect size in perspective, Patzkowski et al., reports effect sizes for FSST, TSA, SSWV-L and 40D of approximately 0.6, 0.7, 1.0 and 1.0, respectively.

Based on the above considerations, the targeted sample size for the study is 85 patients.

10.3 Randomization

N/A

10.4 Missing Data and Measures to Minimize Bias

Missing data is a serious concern that complicates the interpretation of the study results. We will address this issue from both a study conduct and analysis perspective. Regarding study conduct, we will:

1. Limit participant burden and inconvenience in data collection
2. Select high quality investigators
3. Provide pre-study training of investigators as well as on-study reinforcement
4. Reimburse investigators based on follow-ups completed not on per-patient basis.
5. Monitor and report missing data rates during the study
6. Emphasize the importance of full participation in the study during the consent process.
7. Collect information on the reasons for missing data.
8. Actively engage participants and educate them about the importance of participation
9. Hold regular Protocol Committee meetings to discuss strategies for follow-up
10. Set targets for acceptable rates of missing data and terminate sites not meeting targets.

While these efforts will help to minimize missing data, we recognize that missing data is inevitable. With this in mind, we will conduct sensitivity analyses to evaluate the robustness of the study results to various untestable assumptions about the missing data mechanism. In addition to unadjusted analyses, which rely on the missing completely at random assumption (testable), we will also estimate treatment effects (utilizing relevant auxiliary information) under the missing at random assumption. Further, we will explore the effect of departures from the missing at random assumption using pattern-mixture and selection modeling techniques.

10.5 Planned Interim Analysis
N/A

10.6 Analysis Plan
All analyses will be conducted under the supervision of our senior statistician, Dr. Daniel Scharfstein and METRC's senior economist, Dr. Greg Delissovoy.

Specific Aims #1 and #2: Assessing Immediate and Long-term Improvements in Functional Performance and Self-Reported Outcomes. As described above, one-sided paired t-tests will be used to test for improvements in outcomes at a specified point in time after enrollment as compared to baseline. Differences in means between follow-up and baseline will be reported along with 95% confidence intervals.

To the extent possible, we will explore how improvement correlates with characteristics of the participants, the type and extent of their injury, baseline measures of impairment, and the percent of pre and post IDEO PT sessions attended (as we expect some variation in adherence to the PT regimen). Differences in improvement will be examined using stratified analyses and regressions where the change in outcomes is the dependent variable. We will also conduct the analysis including and excluding participants who complete less than 1/3 of the PT sessions.

Specific Aim #3: Documenting Patterns of Use and Satisfaction with the IDEO. This aim is largely descriptive in nature. To the extent possible, patterns of use and satisfaction will be compared with other studies reported in the literature. Also, variations in device satisfaction will be modeled as a function of patient characteristics and baseline measures of impairment using the appropriate regression techniques.

Specific Aim #4. Assessing the Economic Impact of PRIORITI. Relative to standard of care (SOC), the PRIORITI program may increase or decrease costs of care. Provision of the IDEO device, the associated rehabilitation program, need for special shoe wear, and any adjustments, repairs or replacements needed during the lifetime of wear represent added costs relative to SOC. However, the PRIORITI program could potentially reduce certain types of resource use and costs relative to SOC. For example, if the IDEO device offers greater mobility (without use of ambulatory aids) or reduced pain, participants might decrease follow-up visits or use of pain medications relative to standard of care. Use of the IDEO could also lead to fewer delayed amputations. Labor force participation, return to duty, and productivity of participants enrolled in

the PRIORITI program could also improve relative to SOC and this has economic benefit from both the patient and societal perspectives.

Our analysis of the costs and benefits of PRIORITI will involve two components: (1) analysis of costs and outcomes as observed during the 12-month study period; and (2) cost-effectiveness projected over the patient lifetime. 12 Month Costs and Outcomes Difference in one-year cost for the PRIORITI group relative to standard of care will be evaluated based on difference in means. Confidence intervals for difference will be estimated using a bootstrapping procedure that is robust for the anticipated right-skewed distribution of costs. If average cost is greater for the PRIORITI group, a cost-effectiveness ratio will be calculated using a metric such as incremental cost per unit change in Short Form Musculoskeletal Function Assessment (SMFA), or incremental cost per unit change in VR-12.

Lifetime Cost-Effectiveness. If superior to standard care, the PRIORITI program could have a major impact on the patient's long-term functional status and quality of life. To gain insight on this proposition, a cost-effectiveness model will be constructed that simulates the long-term course for two identical patient cohorts, IDEO and standard of care. Model parameters will be derived from the study data, literature review, and expert opinion. Markov modeling will be used in order to characterize patient health state over time. For example, a small portion of patients who initially undergo limb reconstruction, later elect amputation. This would represent a change of "health state" in a Markov model and the probability of transition from the "limb reconstruction state" to "amputation state" will be derived from literature review. Similarly, patient preference (utility) for various health states associated with recovery from traumatic injury will also estimated and used to calculate quality-adjusted life years, to be derived suing the VR-6D. Overall findings of this analysis will be stated in terms of incremental cost per quality adjusted life-year for PRIORITI relative to standard of care.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Data Quality Assurance

Quality Control (Q/C) and Quality Assurance (Q/A) procedures that apply to all studies are outlined in the METRC Manual of Operations (MOP). A certification process (also outlined in the MOP) will be used as a basis for training and certification of the study personnel involved in data collection. In addition to consortium wide training and certification procedures, additional requirements may be added based on the nature of the study. Ongoing data edits and audits will be performed to ensure collection of quality data. The continuous and timely flow of data from the centers to the MCC is an essential prerequisite for maintaining data quality. Monthly enrollment reports will be distributed to each center that will summarize recruitment, data completion and timeliness of data entry. These reports will also include a set of queries generated by REDCap and sites will be asked to address these queries within 10 business days.

11.2 Training and Certification of Centers

All participating centers together with their respective study personnel will undergo certification that includes training, local site IRB, and a knowledge assessment on the study design and procedures. Training will include one-on-one brace fabrication training with each site's designated CPO, RTR program training with each site's designated study PTA. In addition, the research coordinators will receive training related to protocol submission, participant recruitment, study implementation, and data collection at the site level**.**

12. ETHICS/PROTECTION OF HUMAN SUBJECTS

12.1 IRB/Ethics Committee

IRB approval will be obtained from the MCC at Johns Hopkins Bloomberg School of Public Health, the DoD, and each participating clinical site according to METRC policies and procedures. Sites that recruit patients will submit METRC study recruitment materials to their organization's IRB prior to use at that facility.

Sites must provide the Coordinating Center with a copy of the initial IRB approval notice and subsequent renewals as well as copies of the IRB approved consent statements.
No site can begin work related to this study until the site has been certified by the MCC in accordance with METRC policies and procedures.

12.2 Exclusion of Women, Minorities, and Children (Special Populations)

The proposed study anticipates recruiting a significant proportion of racial/ethnic minorities (African-Americans, Asian-Americans and Hispanics) as well as non-Hispanic white subjects. The study will not include children or prisoners.

12.3 Participant Confidentiality

It is the investigator's responsibility to conduct the protocol under the current version of Declaration of Helsinki, ICH Guidelines, Good Clinical Practice, and rules of local IRBs. The investigator must ensure that the patient's anonymity be maintained in their data submission to the Data Coordinating Center.

Patients will be identified only by an identification code but not by their name, SSN, or hospital medical record number. Study Site Investigators will maintain a separate confidential enrollment log, which matches identifying codes with the patients' names and addresses available only to local clinic staff certified by the MCC to participate in the study.

All study forms, reports, and other records that are part of the study data collection materials will be identified by coded number to maintain patient confidentiality. All paper records will be kept in locked file cabinets. All electronic records of study data will be identified by coded number. Clinical information will not be released without written permission of the patient, except as necessary for monitoring by the sponsor (MCC), IRB, DOD, or DSMB. Consent procedures and forms, and the communication, transmission and storage of patient data will comply with

individual site IRB and DOD requirements for compliance with The Health Insurance Portability and Accountability Act (HIPAA).

12.4 Study Discontinuation

Participants will be informed that they may discontinue the study at any time, for any reason. They will be assured that the medical care, which they receive at the participating facility will not be affected should they elect to discontinue participation in the study.

13. DATA HANDLING AND RECORD KEEPING

13.1 Data Management Responsibilities

Instructions concerning the recording of study data on case report forms will be provided by the MCC. Each study site is responsible for transmitting the data in a timely fashion.

The research coordinators at each site will obtain the information necessary to complete the case report forms (CRFs) from several sources including but not limited to, the patient's medical record, clinical evaluations and patient interviews. These forms will NOT contain the patient's name, SSN, or hospital medical record number; they will be identified only by a unique patient-specific study number.

The Site Research Coordinator will enter non-personally identifiable information into a central and secured web-based data management system being implemented for all Consortium studies, known as REDCap. This data management system has incorporated state-of-the-art features for electronic data collection and is configured in accordance with best practices for information technology and research data management.

All research data, in hard copy or electronic form, will be stored and managed in a secure manner following applicable federal regulations and ICH guidelines and according to institutional policies and practices. Hard copy documents containing subject data, patient identifiers and contact information will be stored in secure, locked containers (file cabinets, drawers, etc.) in accordance with standard document management practices.

At all times only MCC-certified key personnel specifically designated and authorized by the Principal Investigator shall have access to any research related documents, including electronic data and medical records. All such personnel will be properly trained and supervised regarding the management and handling of confidential materials. The Principal Investigator assumes full responsibility for such training, supervision, and conduct. This information will be available for audit by study monitors and representatives of the local IRB, the MCC, the DOD, and the OHRP.

13.2 Data Capture Methods

Data will be collected in real time by the investigator or study coordinator directly on paper Case

Report Forms (CRFs), which will serve as source documents for the study. Source documents, which will include both the CRFs and other supporting medical records (e.g radiology reports, clinical notes and discharge summaries), will be signed by PI, other site Investigator, or Research Coordinator as indicated in the CRF instructions. The Research Coordinator or an MCC-certified staff member working under the supervision of the research coordinator, will enter the data from the CRFs into the REDCAP database.

13.3 Types of Data

Data will include medical and surgical histories, radiology reports, clinical evaluations, performance assessments, adverse events and patient interviews.

13.4 Source Documents and Access to Source Data/Documents

Source documents including CRFs, radiographic reports, patient surveys, medical records, etc. will be maintained at the site and will be made available to study monitors, and representatives of regulatory agencies including the MCC, DOD, IRB, and OHRP.

13.5 Study Records Retention

Study records will be maintained in accordance with current ICH guidelines. Data will be maintained for five years following the end of research-related activities. At the end of this period, each site will provide the Coordinating Center a signed verification that these data have been destroyed.

13.6 Protocol Deviations

Records of protocol deviations will be noted on the Protocol Deviation CRF (AF05) with the reason for the deviation recorded, as well as any action taken to mitigate the deviation. This information will be entered into REDCap. These records will be provided to the site's IRB in accordance with local reporting requirements and be made available to study monitors.

14. PUBLICATIONS POLICY

Publications will be written in accordance with the METRC publication policy (available on the METRC website: www.metrc.org).

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17. APPENDICES

APPENDIX A: STUDY CONTACT ROSTER

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APPENDIX B: PROTOCOL COMMITTEE

Ellen MacKenzie, PhD	Johns Hopkins Bloomberg School of Public Health
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LTC Donald A Gajewski, MD	Center for the Intrepid, San Antonio Military Medical Center
John Ferguson, CPO	Center for the Intrepid, San Antonio Military Medical Center
Johnny G. Owens, MPT	Center for the Intrepid, San Antonio Military Medical Center
Rebecca Hooper, PT, PhD	Center for the Intrepid, San Antonio Military Medical Center
CDR David Dromsky, MC	Naval Medical Center San Diego
Capt Jennifer L. Town, NC	Naval Medical Center San Diego
Kevin Kuhn CDR, MC	Naval Medical Center San Diego
Robert Sheu, LDCR, MC	Naval Medical Center San Diego
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COL (ret) Charles Scoville, PT	Walter Reed National Military Medical Center
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Daniel Scharfstein, PhD	Johns Hopkins Bloomberg School of Public Health
Jennifer DeSanto, RN, MS	Johns Hopkins Bloomberg School of Public Health
Gregory Delissovoy, PhD	Johns Hopkins Bloomberg School of Public Health

APPENDIX C: DATA COLLECTION SCHEDULE

	TIME 0	T2	T3	T4
Assessment	**Baseline**			
Patient Characteristics				
Demographics	X			
Marital Status &Social Support (MSPS)	X			
Self Efficacy	X			X
Income (past year) & Health Insurance	X			X
Injury Characteristics				
Mechanism, Type, Side of Injury	X			
Classification of Fx (AO/OTA & Gustilo)	X			
Other limb and non limb injuries	X			
Medical History and Clinical Assessment				
Height and Weight	X			X
Co-morbidities & Smoking History	X			
Fracture Healing	X			
Evidence of PTOA (from x-rays)	X			
ROM and Strength of Lower limbs	X			X
VAS Pain and Use of Narcotics	X			X
Outcomes: Performance Assessments				
4 Square Step Test	X	X		X
Illinois Agility Test	X	X		X
Sit to Stand	X	X		X
Timed Stair Ascent	X	X		X
Self Selected Walking Speed	X	X		X
Shuttle Run	X	X		X
Single Leg Stance	X	X		X
Outcomes: Self Reported Measures				
Short Musculo Func Assess (SMFA)	X		X	X
Veterans Health Survey (VR-12)	X		X	X
Paffenbarger Activity Scale (PPAQ)	X			X
Brief Pain Inventory (BPI)	X			X
Usual Major Activity Status	X		X	X
If working: Work Productivity (WPAI)	X		X	X
Depression Scale of PHQ (PHQ-9)	X			X
PTSD Checklist (PCL)	X			X
Use and Satisfaction with IDEO				
Satisfaction with Brace (OPUS & CFI)	X	X	X	X
Use of Brace, Shoe Wear , Ambulatory Aids	X	X	X	X
Use of Services and Aids				
Hospitalizations	X		X	X
Orthotic Services	X		X	X
PT/OT Services	X		X	X
Other Services	X		X	X
Treatment Logs Maintained by CPO & PTs				

APPENDIX D: CONSENT TEMPLATE

INFORMED CONSENT DOCUMENT

Participant Consent Form

Study Title: Patient Response to an Integrated Orthotic and Rehabilitation Initiative for Traumatic Injuries (PRIORITI-MTF)

Principal Investigator: Ellen MacKenzie, PhD

IRB No.: 00005172

PI Version Date: Version 6; 12/05/14

You are being asked to volunteer to be a part of a research study. Please read this form carefully before you sign it. This consent form explains the research study and your part in the study. If you decide not to participate in this study there will be no impact on your medical care. You can choose not to take part and if you join, you may quit at any time. Ask the study doctor or the study staff to explain any words or procedures that you do not clearly understand. Ask as many questions as needed. All of your questions should be answered to your satisfaction before you sign this form.

1. WHAT IS THE PURPOSE OF THIS RESEARCH STUDY?

This research is being done to help determine whether a new type of custom designed brace along with a physical therapy program improves your physical function. Further, the study is a clinical investigation to evaluate the effectiveness of an investigational FDA-regulated medical device. The device being used in this study is the IDEO brace. Because we are testing this device in the study, it will be labeled with the following information: "***CAUTION--Investigational device. Limited by Federal law to investigational use***."

This brace was developed for wounded warriors who wanted to return to an active lifestyle. Early studies showed that wounded warriors who received the brace and participated in the physical therapy program had better function than before they had the brace. The purpose of this study is to see if the brace along with therapy will improve function and return to usual activities in people with lower leg, ankle or foot injuries like yours.

This PRIORITI study is funded by the Department of Defense (DOD) and is being carried out in three Military Treatment Facilities that are taking care of service members who are injured in the line of duty.

2. WHY AM I BEING ASKED TO PARTICIPATE?

You are being asked to participate in this study because you had a traumatic injury of the lower leg at least 1 year ago and you are still limited in the activities you are able to do. People with injuries like yours from around the county are being asked to participate. You are one of 90 patients we are asking to join the PRIORITI study.

3. HOW LONG WILL THE STUDY LAST?

Your participation in the study will be expected for one year.

4. HOW DOES THE STUDY WORK?

After you review this informed consent and agree to be part of the study, the following things will happen:

- You will be asked questions about you and the activities you do now. These questions could take up to 15 minutes to answer.
- Information will be collected about your injury and the care you received for your injury. A member of the research team will enter this information into a database.
- You will receive a clinical assessment to measure in your leg weakness and how well you can bend your foot. The assessment could take up to 15 minutes.

If the surgeon feels that you are still eligible based on the clinical assessment you will be scheduled to return to the clinic to begin the PRIORITI program that includes up to 8 weeks of physical therapy (PT) sessions. Each week for the first 2-4 weeks, you will receive a home physical therapy program as prescribed by the study team. The length of the home physical therapy program is dependant on the time required to fabricate the IDEO™. In addition, you will be fitted for the brace. Before the first PT session, you will be asked to complete several performance tests to measure your current physical performance. Performance testing at each interval below could take up to 30 minutes of your time. A member of the research team will time you to see how long it takes for you to:

- walk the length of a long hallway
- repeatedly rise from a chair
- climb a set of stairs
- balance on one foot
- change direction while stepping over a small obstacle
- run or walk as fast as possible between two cones

During the first 2-4 weeks you may be asked to return to the center for a test fitting, prior to receiving the completed IDEO™. , After you receive the IDEO™ you will be asked to come back to the study center for 4 weeks of PT. Each week, you will receive 3 sessions of PT lasting approximately 90 minutes. These sessions will teach you how to use your brace and get the most out of wearing the brace. At the end of the 4 weeks of therapy, you will be asked to repeat the performance tests once again.

After you have completed the physical therapy program, you will be given the phone number of the orthotist to call if you have any concerns or problems with your brace when you are at home. At 6 months after completing the program, you will be called by the Research Coordinator for a brief interview. The Research Coordinator will ask about your function and satisfaction with the brace and about health care services you have used.

During the final study visit at 12 months following completion of the PRIORITI program, you will be asked to return to the study center and complete the performance tests one more time and answer questions about your function and satisfaction with the brace. This could take up to 45 minutes of your time.

5. WHAT ARE THE POTENTIAL RISKS OR DISCOMFORTS?

There is a small possibility that you may injure yourself during the PT sessions. These sessions will be performed under close supervision by a trained physical therapist and will be geared toward your ability level.

There also may be a small risk of falling during the performance tests. The tests are given in order of difficulty. If you can't perform the tests of lower difficulty, you will not be asked to perform more difficult tests. If you don't feel comfortable doing any of the tests, you can stop at any time.

There is also a chance that your function and quality of life may not improve. This may be disappointing to you.

Any time information is collected for a study there is a small risk of breach of confidentiality. As described below, your research data will be identified by a unique study number rather than your name and all measures allowed by law to protect your confidentiality will be taken by the research staff.

In this study, you will be exposed to a small amount of radiation called "ionizing radiation," which is like x-rays. Studies have shown that getting a lot of radiation at one time or getting many small doses over time may cause cancer. The risk of getting cancer from the one small radiation dose in this study is very small.

Tell us now if you have been in other research studies where you had ionizing radiation. Also tell us if you have been exposed to radiation in other ways, like on your job or in radiation therapy.

What if you are pregnant? If you are pregnant or nursing, you cannot be in this research study because the radiation may harm your baby.

6. WHAT ARE THE POTENTIAL BENEFITS?

As a result of participating in this study, your physical function, quality of life and performance of daily activities may improve. Furthermore, your participation in the study could help us determine the best treatment for injuries like yours. This information could be very helpful to other people who have this same injury in the future.

7. DO I GET ANY PAYMENT FOR BEING IN THE STUDY?

Active duty military personnel will not be paid to participate in the study.

If you are not on active military duty you will receive a total of $300 for your participation in the study. The $300 will be provided to you according to the following schedule:

- $50 at the time you enroll in the study and complete the baseline assessments.
- $75 when you complete the home physical therapy (prior to receiving the IDEO™)
- $75 when you complete the 4 weeks of physical therapy (after receiving the IDEO™)
- $100 when you complete the final assessment at 12 months

8. ARE THERE ANY COSTS INVOLVED IN BEING IN THE STUDY?

There is no cost to you to participate in this study. You will not be charged for the brace or the physical therapy. You will not be charged for additional visits to the orthotist during the study period if you have problems with the brace.

9. WILL MY INFORMATION BE KEPT PRIVATE?

The information we collect from you will be kept private to the best of our ability. Your name, birth date, medical record number and any other information that could identify you as an individual will be removed from all study forms. Instead, we will label your forms with a unique study number. The link between your name and your study number will be kept confidential to the greatest extent provided by law. The information collected for the study will be stored in a password protected, HIPAA verified computer database that only authorized members of our research team can use. When we report the results of the study, we will combine the information about you with similar information about hundreds of other people so your individual information will not be identifiable.

All study records will be considered confidential, and your name will not be used in reports or publications.

10. WILL YOU SHARE MY INFORMATION WITH OTHERS?

We will use your information only for the purposes of this study. The data from the study may be published. However, you will not be identified by name. People designated from the institutions where the study is being conducted will be allowed to inspect sections of your medical and research records related to the study. This includes people designated by The Johns Hopkins Bloomberg School of Public Health who are overseeing this study. Everyone using study information will work to keep your personal information confidential. Your personal information will not be given out unless required by law.

The Department of Defense is providing funding to conduct this study. Representatives from the U.S. Army Medical Research and Materiel Command (USAMRMC) Office of Research Protections (ORP) Human Research Protections Office (HRPO) and your local IRB may have access to research records in their role to protect human subjects engaged in research.

11. WHAT ARE MY ALTERNATIVES TO PARTICIPATION?

Your alternative is to not take part in the study. If you choose not to take part, your healthcare will not be affected.

12. WHAT HAPPENS IF I LEAVE THE STUDY EARLY?

Your participation in this study is completely voluntary. You have the right to withdraw from the research study at any time without penalty. Your decision will not affect the medical care you receive. If you decide to stop participating, you should notify the study doctor or the research coordinator at your center.

Your participation in this research study could be ended without your consent. Possible reasons could include our decision to end the study early or other reasons.

13. WHAT HAPPENS IF I AM INJURED OR BECOME ILL BECAUSE I TOOK PART IN THIS STUDY?

If you are injured or become ill because of your participation in this study, you will receive emergency medical care if needed and you will receive assistance in getting other medical care as needed. You or your insurance carrier will be billed for the cost of care, just as you would be

billed for any other medical care. If you have any costs that are not covered by insurance, they are your responsibility.

You do not give up any of your legal rights by signing this form. You can seek legal compensation for any injury that may occur to you during the study as a result of an error by a member of the research staff or others.

14. WHO DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

- <<insert name>>, the study coordinator at your hospital has discussed this information with you and offered to answer any questions you may have. If you have further questions or get sick or injured as a result of being in this study, you can contact << insert him/her>> at <<telephone number>>. You may also call the Director of the Study at your hospital, <<insert name>>, at <<telephone number>>.

- If you have further questions about your rights as a study participant you can call or contact your local IRB office or the Johns Hopkins Bloomberg School of Public Health IRB Office. The Johns Hopkins Bloomberg School of Public Health is serving as the overall coordinating center for this study that is being conducted in hospitals around the country. Contact the Johns Hopkins IRB if you feel you have not been treated fairly or if you have other concerns. The IRB contact information is:

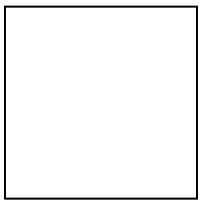
You will receive a copy of this signed consent form.

What does your signature (or thumbprint/mark) on this consent form mean?

Your signature (or thumbprint/mark) on this form means:

- You have been informed about this study's purpose, procedures, possible benefits and risks.
- You have been given the chance to ask questions before you sign.
- You have voluntarily agreed to be in this study.

_____	_____	_____	___:___
Print name of Adult Participant	Signature of Adult Participant	Date	Time



Ask the participant to mark a “left thumb impression” in this box if the participant (or participant’s parent) is unable to provide a signature above.

_____	_____	_____	___:__
Print name of Person Obtaining	***Signature of Person Obtaining Consent***	***Date***	***Time***

APPENDIX E: EVALUTION TO GIVE CONSENT

EVALUATION TO GIVE CONSENT

Procedure: Make a subjective judgment regarding item 1 below. Ask questions 2 through 4. You may select the language to use in asking the questions in order to help the respondent understand them.

1. Is the respondent alert and able to communicate with you?

   Yes ___ No ____ (if condition not likely to change, seek proxy consent)

2. Ask the respondent to name at least one thing that s/he will be asked to do as part of the study.

   *Describe*_____
   _____

3. Ask the respondent to explain what s/he could do if s/he decided s/he did not want to participate in the study.

   *Describe*_____
   _____

4. Ask the respondent to explain what s/he would do if s/he were experiencing distress or discomfort at any time during the study.

   *Describe*_____
   _____

I hereby certify that the above-named respondent is alert, able to communicate, and able to give acceptable answers to items 2, 3, and 4, above.

_____ _____
Research Coordinator Date

APPENDIX F: BROCHURE INSERT

Be part of the PRIORITI -MTF Team!
Help advance limb trauma care through research.

What is the PRIORITI-MTF Study?
The goal of the PRIORITI-MTF study is to help determine whether a new type of custom designed brace, called the IDEO ™ along with a physical therapy program, called Return to Run, improves your physical function.

Why me?
The PRIORITI-MTF study is funded by the Department of Defense (DoD) and is being carried out in three Military Treatment Facilities across the United States that are taking care of service members who were injured in the line of duty.

You are being asked to participate in this study because you had a traumatic injury of the lower leg at least 1 year ago and you are still limited in the activities you are able to do. Service members with injuries like yours from around the country are being asked to participate.

How does the study work?
If you are eligible for the study and agree to participate, the following things will happen:

- You will be asked questions about you and the activities you do now.
- Information will be collected about your injury and the care you received for your injury. This information will be entered into a database by a member of the research team.
- You will receive a clinical assessment to measure your leg weakness and how well you can bend your foot.
- You will be measured for the IDEO™ brace and begin a home physical therapy (PT) program while the IDEO™ is being made.
- You will be fitted for the IDEO™ and will participate in 4 weeks of physical therapy with the brace.
- You will be asked to participate in performance testing at several intervals: at baseline, after the 4 week Return to Run PT program and at one year following completion of the program. At these times we will also ask you questions about your functioning and satisfaction with the device.
- After the end of the program, the IDEO™ is yours to keep.

We hope you will consider taking part in the PRIORITI-MTF Study. It is a way to be part of a nationwide effort to help advance limb trauma care for others in the future. Please talk to your doctor about participating, or email us at prioriti-mtf@metrc.org. You can also visit www.prioriti-mtf.org or www.METRC.org to learn more.

APPENDIX G: Draft Radio Script

Have you sustained an injury to your lower leg while in the military 1 or more years ago? Does this injury prevent you from performing your day to day activities and engaging in sports and other recreational activities? If so, you may be eligible to participate in a research study to evaluate a new brace for lower leg injuries. Qualified participants will receive study related orthopedic evaluations, receive a new orthotic brace and participate in a four week physical therapy program at no charge. If you are interested please visit www.prioriti-mtf.org for more information or call 410-614-3723.

Appendix H: Sample Letter from Physicians to potential participants:

Dear *(Colleague)*

I am reaching out to you to give you some information about a study that is being done locally that could impact some of your patients. The research is being done to help determine whether a new type of custom designed brace called the IDEO along with an intense physical therapy program called the Return to Run Program improves your patient's physical function. The IDEO was developed for wounded warriors who want to return to an active lifestyle, including active duty.

The study is for patients who have had an injury to their lower leg and are one or more years out from their injury. We are looking for patients with unilateral injuries who are healed (will not require further surgeries within the next 6 months) and able to fully bear weight. They must also meet the following criteria:

Evidence of either:

- Weakness of ankle dorsiflexors and /or plantarflexors resulting from leg injury (defined as less than 4 out of 5 on manual muscle test)
- Limited ankle dorsiflexion (< 10 degrees) and /or limited ankle plantarflexion (< 20 degrees) resulting from leg injury
- Mechanical pain with loading to hindfoot/midfoot (>= 50 mm on a 0-100 mm visual analogue scale assessing average daily pain)
- Ankle or hindfoot fusion or candidate for ankle or hindfoot fusion
- Candidate for amputation secondary to ankle/foot impairment

If you feel that you have patients who meet the above criteria, please provide them with the enclosed brochure and contact information. You may also refer them to our website: www.prioriti-mtf.org. If you have questions please feel free to reach out to me *(Site PI name) or (Site PI Coordinator name)* using the following contact information *(phone number, email)*. You can also visit www.prioriti-mtf.org to learn more. We appreciate your consideration in referring your patients to this study.

(Signed by Treating Physician)

Appendix I: Study Video [DRAFT]

Narrative	**Suggestions for Visuals**
You are watching this video because you had a bad injury to your lower leg one or more years ago. Although this type of injury is rare in everyday life, it is quite common among members of the military. For this reason, the United States Department of Defense is funding research to help us determine the best way to treat these injuries. The goal of this research is to help wounded service members and veterans like you recover from severe leg injuries and return to the activities they enjoy doing. We are asking you to consider participating in this research today to help others like you in the future. The name of this research study is the PRIORITI study. This video will give you more information to help you decide if you would like to participate in the study. The goal of the PRIORITI study is to evaluate the benefits of a new brace for the lower leg. This brace is called the Intrepid Dynamic Exoskeletal Orthosis or the IDEO brace.	PRIORITI study logo Image of service members Image of severe open fracture of the tibia Image of IDEO
Right now there are braces called ankle foot orthoses, or AFO's, that have been made for people with different needs. They provide support to the ankle where there might be weakness. Most of these braces, however, are static or have no moving parts. Other braces, like the IDEO brace, have been made to provide support but also incorporate a strut that acts as a spring. The strut is intended to act as an energy storing device, which is meant to help provide a balance of power in the muscles of the	Images of braces Image of IDEO

lower leg and ankle. The brace is intended to assist in increasing the speed and quality with which you can walk and return to vigorous activities like running.	
This brace was developed by a team at the Center for the Intrepid in San Antonio, TX Some research has been done using the brace along with a physical therapy program called the Return to Run or RTR program. The multidisciplinary Return to Run (RTR) clinical pathway focuses on strength, agility and speed with the goal of enabling patients to return to running, sports and military deployment. For the purpose of this study, we would like to re-create this program and test it closer to where you live. This is why we need people like you to participate. We would like to further evaluate the IDEO brace along with the RTR program outside the place where it was created. ENTER DR X. You are being asked to participate in the PRIORITI study because your doctor has determined that you could potentially benefit from wearing the IDEO. The type of injury you sustained is fairly uncommon, so the study's success depends on people with injuries like yours from major trauma centers across the country joining together to take part in this effort. If you choose to participate in this study you will be asked to do the following: Step 1: To determine if you can be in the study • You will be asked questions about you and the activities you do now • Information will be collected about your injury and the care you received for your injury. This information will be entered into a database by a member of the research team.	Images of CTI, Ryan, Etc? Images of PT, Running w brace, RTR Group

• You will receive a clinical assessment to measure in your leg weakness and how well you can bend your ankle. Step 2: The Study Itself If the surgeon feels that you are eligible based on the clinical assessment you will be scheduled to return to the clinic to begin the PRIORITI program. The program includes 8 weeks of physical therapy (PT) sessions …. 4 weeks before you get the brace and 4 weeks after you have been fitted and are wearing the brace. <u>Physical Therapy</u> You will recieve a home physical therapy program from your study team. You will perform the exercises as directed for each of the first 4 weeks. Before the first PT session, you will be asked to complete several performance tests to measure your current physical performance. A member of the research team will also time you to see how long it takes for you to: • walk the length of a long hallway • repeatedly rise from a chair • climb a set of stairs • balance on one foot • change direction while stepping over a small obstacle • run or walk as fast as possible between two cones These tests will be repeated at different times over the course of the study.	
<u>IDEO Brace</u> The brace will be custom made for you by a Certified Prothestist/Orthotist or CPO in the prosthetics lab at your base hospital.	Video of brace measuring, fitting etc.
Physical Therapy Again… After the first 4 weeks of physical therapy, you will be asked to repeat the physical performance tests. At this time you will receive the brace and will be asked to come back to the study center for another 4 weeks of PT. Each week, you will receive 3 sessions of PT lasting approximately 90 minutes.	More images of PT

These sessions will teach you how to use your brace and get the most out of wearing the brace. At the end of the 4 weeks of therapy, you will be asked to repeat the performance tests once again.	
Finally, during the final study visit at 12 months following completion of the PRIORITI program, you will be asked to return to the study center and complete the performance tests and answer questions about your function and satisfaction with the brace.	Performance test pics
We hope that the description of the IDEO brace and the RTR program has helped you better understand the study. We hope to show if this brace is beneficial in improving function following a severe injury like yours. Our goal is to help people with these severe injuries recover and get back to doing what they enjoy most in life. If you have questions about these treatments or the study, please ask your surgeon or study coordinator at the end of the video. Thank you for considering taking part in the PRIORITI study. Previous research volunteers have provided us with tremendous knowledge that will directly benefit you in the care we give you today. We are asking you to consider participating to help civilians and injured service members in the future. If you decide to join PRIORITI, know that you will be helping to shape the future of trauma care. Thanks again for learning more about the PRIORITI study, and we wish you the best in your recovery.	Images of patients More images of service members Thank you!

Appendix J: Draft Study Announcement

RESEARCH STUDY FOR ADULTS WITH DECREASED LOWER LEG FUNCTION

We are looking for volunteers to take part in a study to evaluate a new brace for military personnel who have had an injury to their lower leg 1 or more years ago, resulting in a loss of function.

You may qualify if you are 18 years or older, are at least 1 YEAR past your injury and can answer yes to one or more of the following questions:

- Are you limited in what or how much you are able to do at home, at work or at school because of your leg injury?
- Are you limited in the types or frequency of sports and recreational activities you would like to do because of your leg injury?
- Are you dissatisfied with the recovery you have made from your leg injury?

Qualified participants will receive study related orthopaedic evaluations, will be fitted for and receive the new orthotic brace, and participate in 8 weeks of physical therapy at no charge to you. Military personnel who are not on active duty will receive compensation for time and travel. Assistance with transportation is available.

For more information please call:

(XXX) XXX-XXXX

Contact Site PI

Principal Investigator

Contact Site Coordinator

Research Coordinator

This study has been reviewed by, and received ethics clearance through, (your institutional research office name, location).

Appendix K: Research Coordinator Script for 6 Month Visit

The following will be read to the participant during the 6 month follow up phone call:

The study is able to cover the expense of your transportation to and from the center for the 12 month follow up visit. Accommodations for one night will be covered if you are unable to travel to and from the center in one day. We will cover up to 50/day for meals for a maximum of 2 days.

After mentioning the reimbursement plan, the coordinator will make arrangements per institutional policy and inform the coordinating center.