



**CDMRP**  
DEPARTMENT OF DEFENSE  
CONGRESSIONALLY DIRECTED  
MEDICAL RESEARCH PROGRAMS

# Peer Reviewed Orthopaedic Research Program



Optimizing Recovery and Restoration of Function

For more information, please visit  
[cdmrp.health.mil/prorp](http://cdmrp.health.mil/prorp)

# CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS

## HISTORY

The Congressionally Directed Medical Research Programs, CDMRP, was created in 1992 from a grassroots effort led by the breast cancer advocacy community that resulted in a congressional appropriation of funds for breast cancer research. This initiated a unique partnership among the public, Congress, and the military. Since then, the CDMRP has grown to encompass multiple targeted programs and has managed over \$19.4 billion since its inception through FY22. Congress provides overarching intent for each individual program, such as the Peer Reviewed Orthopaedic Research Program, PRORP, and specifies the funding amount as part of the annual DOD Appropriations Bill.

## APPLICATION REVIEW PROCESS

The CDMRP uses a two-tier review process for evaluating applications that involves dynamic interaction between scientists, consumers from advocacy communities, clinicians, members of the military, and other specialists as applicable. The first tier of evaluation is a scientific peer review of the applications, measured against established criteria for determining scientific merit. The second tier is a programmatic review by the Programmatic Panel, which compares applications to each other and makes recommendations for funding based on scientific merit, potential impact, adherence to the intent of the award mechanism, relevance to program goals, and portfolio composition.



*\*pending Congressional appropriation*



“Serving as a Consumer Reviewer on the PRORP Peer review and [now] the Programmatic review process I use my years of experience being a combat injured Veteran to speak for the end user. Shortly after my traumatic amputation I learned of the new and experimental surgical interventions, medical devices and medical techniques and technologies that were used to save my life and give me the quality of life I currently enjoy. I chose to use my experience and daily living with a disability to help others.”

**Sgt. 1st Class Daniel Metzdorf,**  
U.S. Army Retired,  
Programmatic Panel Member (FY22- FY23)

# PEER REVIEWED ORTHOPAEDIC RESEARCH PROGRAM

## ABOUT THE PROGRAM

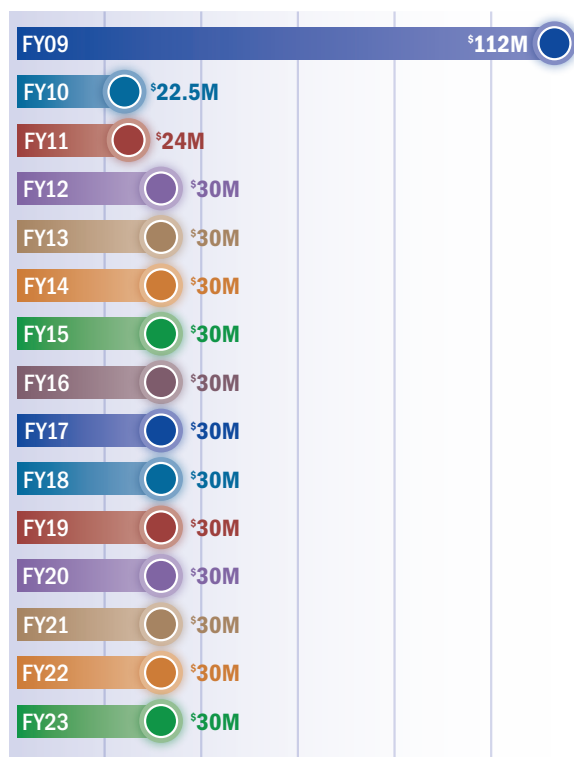
The PRORP was initiated in FY09 with a total congressional investment of \$112 million from two appropriations acts: \$61M from the Consolidated Security, Disaster Assistance, and Continuing Appropriation Act and \$51M from the Supplemental Appropriations Act. The congressional language directed the PRORP to fund “orthopedic and other trauma research, treatment and rehabilitation including regenerative medicine. This funding will continue and expand the existing orthopedic trauma research program, amputee rehabilitation and reset research, and restoration of function.” Since FY09, Congress appropriated a total of \$518.5M to the program, supporting 355 high-impact and clinically relevant research awards that have or will advance the optimal treatment and rehabilitation for Service Members, Veterans, and civilians who sustained orthopaedic injuries.

Orthopaedic injuries profoundly impact military readiness and return to work/activity/duty. Approximately 78% of male and 85% of female Army personnel that separate from active service due to disability are a result of musculoskeletal injuries or conditions. In the general populations, 70% of musculoskeletal injury patients report lost work days, which is a significant impact to the economy in addition to the \$176.1 billion per year cost to treat these injuries.<sup>1</sup> The PRORP strives to find solutions that improve outcomes by funding high-risk/high-reward research projects, translational research that moves the field forward, and clinical trials that move promising interventions into the clinic.

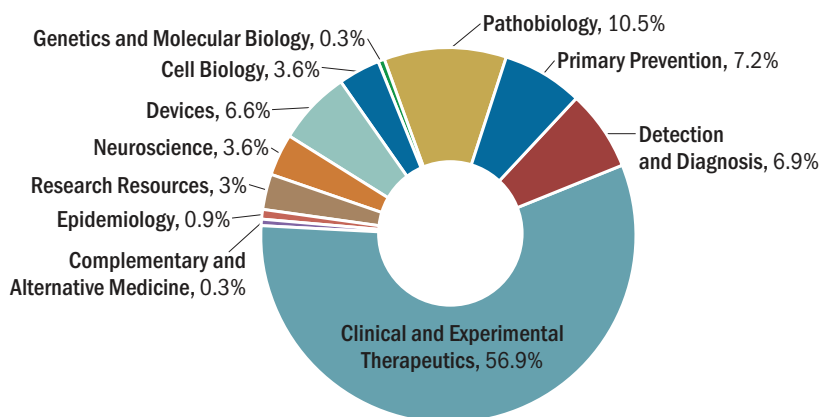
**VISION:** Provide all military Service members with orthopaedic injuries the opportunity for optimal recovery and restoration of function

**MISSION:** Address the most significant gaps in care for the leading burden of injury and for facilitating return-to-duty by funding innovative, high-impact, clinically relevant research to advance optimal treatment and rehabilitation from musculoskeletal injuries sustained during combat and Service-related activities

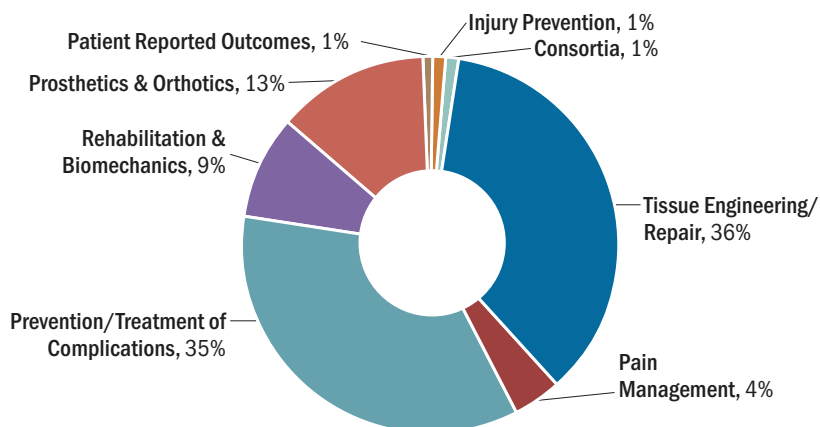
**FY09-FY23 Appropriations**



**FY09-FY21 Portfolio Investment**



**FY09-FY21 Research Portfolio Areas**

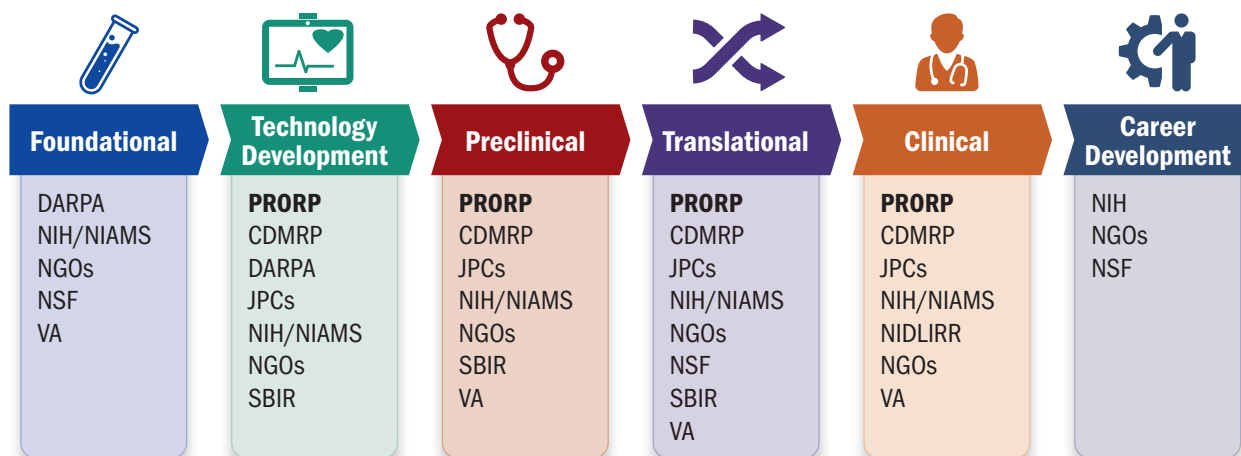


<sup>1</sup> Piccirillo AL, Packnett ER, Cowan DN, Boivin MR. 2016. Risk factors for disability discharge in enlisted Active Duty Army soldiers. Disabil Health J. 9(2):324-331.



# COORDINATION WITH OTHER AGENCIES AND PARTNERS

The PRORP team hosts an annual vision setting meeting during which the PRORP Programmatic Panel, comprised of military, consumer, and civilian subject matter experts in the orthopaedic field discuss the state of the science, stakeholder needs, and historical areas of investment by the program and other funders. Based on these discussions, the Programmatic Panel develops a recommended investment strategy to fill critical research gaps and meet program goals. In addition to recommendations from the PRORP Programmatic Panel, program staff solicit input from the Service branches and experts in several related disciplines during Stakeholder meetings and engagements at professional society meetings. These engagement opportunities allow the program to keep abreast of the ever-changing research landscape and clinical environment for the military and general population. The PRORP also routinely monitors research supported by other federal and non-federal funding agencies, including but not limited to, DOD, the National Institutes of Health, Department of Veterans Affairs, Extremity Trauma and Amputation Center of Excellence, Small Business Innovation Research, National Science Foundation, Society of Military Orthopaedic Surgeons, Orthopaedic Research and Education Foundation, Orthopaedic Research Society, American Academy of Orthopaedic Surgeons, and American Academy of Orthotists and Prosthetists. Through the program's analysis of the funding landscape, the PRORP addresses knowledge and capability gaps by coordinating research funding and priorities across organizations, eliminating research duplication, and ensuring funded efforts are complementary in order to best address knowledge and capability gaps. Several organizations fund orthopaedic-relevant foundational research, and many set aside additional funds to promote career development to maintain and grow the number of researchers in this field. The PRORP aims to have the greatest impact by funding orthopaedic injury and trauma research in the technology development, preclinical, translational, and clinical areas. The following sections of this Program Book illustrate PRORP's efforts in these areas.



*DARPA, Defense Advanced Research Projects Agency; JPCs, Joint Program Committee; NGOs, Non-government Organizations; NIAMS, National Institute of Arthritis and Musculoskeletal and Skin Diseases; NIDILRR, National Institute on Disability, Independent Living, and Rehabilitation Research.*

## PAST

A large majority of combat injuries sustained by armed forces during Operation Iraqi Freedom and Operation Enduring Freedom involved extremity injuries and orthopaedic-specific conditions secondary to battle injury, representing the largest source of long-term disability in returning Service Members. Blast and other combat-related orthopaedic injuries are heterogeneous and complex in nature, typically involving multiple tissues, such as skin, bone, muscle, cartilage, and nerves. The injuries frequently involve multiple limb traumas to an extent not seen in the civilian setting and are sustained in an environment where access to optimal acute care is limited. The complications include, but are not limited to, amputation, infection, compartment syndrome, nonunion of the bone, heterotopic ossification, and temporary or permanent functional muscle loss, among others.

In 2009, the PRORP identified the program's initial goals, to support high-risk/high-gain research projects related to the aforementioned conditions, particularly regarding amputation strategies, limb salvage optimization, prevention of complication, acceleration of healing, enhancement of the tissue environment for healing, restoration of function, and rehabilitation. PRORP funding opportunities specifically solicited research proposals that addressed knowledge and capability gaps in infection, compartment syndrome, non-union, heterotopic ossification, peripheral nerve injuries, muscle function loss, and development of novel assistive devices. The outcomes of these efforts have resulted in new concepts, products, and clinical care guidelines currently in use or in different stages of development, as exemplified in Notable Outcomes on page 5.

# PRESENT

The PRORP currently promotes translational research to advance early discoveries by providing funding to develop treatments and interventions, test efficacy and effectiveness, and support dissemination and implementation into clinical practice. The PRORP supports research along the research pipeline – early in vitro and in vivo research, applied research in animal models, pilot human subjects clinical research, and randomized, controlled clinical trials.

The PRORP funds research in topics pertaining to acute care of battlefield injuries, definitive/reconstructive care, surgical care, rehabilitation, and novel orthotic and prosthetics technologies. Research is increasingly multidisciplinary, and advancements in these areas often benefit from a multi-team approach. The PRORP supports collaborative research and uses research partnership award mechanisms to promote idea sharing and to incentivize innovation and impactful research proposals. These partnerships also created clinical support centers, broadened orthopaedic clinical research expertise, and leveraged military expertise, resources, and capabilities.

## NOTABLE OUTCOMES

The PRORP funded research impacts current and future clinical care paradigms. Some examples include:



A clinical trial, funded in FY09, changed the standard of care for prophylaxis treatment of orthopaedic infection with use of topical vancomycin, resulting in significant reduction in infection risk.



An FY09 clinical trial provides evidence to challenge researchers to reconsider approaches for the prediction of acute compartment syndrome.



The development and validation of the NU-FlexSIV socket, funded in FY09 and FY14, which is offered clinically to support mobility in unilateral transfemoral amputees.



A large rehabilitation consortium, funded in FY10, provided the clinical evidence to support the implementation of rehabilitation techniques now used in military, VA, and civilian clinics around the world.



The SPRINT PNS System from SPR Therapeutics, funded in FY11 and FY17, is now in clinical use as an opioid-alternative for pain treatment following amputation, total knee replacement, and other orthopaedic conditions.



An FY12 clinical trial provided the overwhelming clinical evidence to support use of and surgical training for targeted muscle reinnervation for treatment and prevention of nerve pain in amputees (<https://www.tmrnerve.com/>).



Pivotal research funded in FY13 using clinical samples of osteoarthritis tissues changed the current understanding of the mechanisms and biochemical environment of osteoarthritis onset.



### PRORP PARTNERSHIP-FOCUSED AWARD MECHANISMS, PAST AND PRESENT:

- Career Development Award
- Clinical Consortium Award
- Clinical Translational Research Award
- Clinical Trial Award
- Clinical Trial Development Award
- Integrated Clinical Trial Award
- Orthopaedic Care and Rehabilitation Consortium Award
- Orthopaedic Rehabilitation Clinical Consortium Award
- Translational Research Partnership Award



"I am a 100% disabled Veteran who receives his care from the VA. I have been taking part in these reviews for a few years now and am proud to say I have seen some of

the medical advances we discussed being put into use at the end user level. Albeit a small role in the process, it makes my part even more important knowing that what we do really does make a difference. I am so grateful to be a part of the process in Military and veteran healthcare advances."

**Kent Phyfe,**  
American Legion Post 65,  
(Peer Review, FY19-FY22)

# HIGHLIGHTS OF PRORP-FUNDED RESEARCH



## **Clinician-Friendly Algorithm to Create Low-Cost, Customizable Prosthetic Feet: Biomechanical Evaluation of User-Specific Prosthetic Feet Using the Lower Leg Trajectory Error Framework**

**Amos Winter, Ph.D.**, Massachusetts Institute of Technology

Cutting-edge prosthetic feet continue to push the boundaries of what was once considered possible. Individuals with limb loss can run, jump, and return to daily life with the help of assistive devices. However, the costs of some of the technologically advanced prosthetic devices limit their reach. The concept of low-cost plastic medical devices is not new. However, prosthetists and design engineers need additional information to ensure a plastic prosthetic foot will optimize outcomes for their individual patients. With FY17 funding from the PRORP, Dr. Amos Winter and Dr. Victor Prost, Massachusetts Institute of Technology, and Dr. Matthew Major, Northwestern University, created an algorithm clinicians can use to create low-cost, plastic prosthetic feet customized to patients' body weight and size to induce desired walking biomechanics. In a limited clinical trial, the researcher asked five below-knee amputees to choose their preferred prosthetic foot among three options: their own prosthetic foot, an energy-storing prosthetic foot, and a low-cost, plastic, passive foot designed using their algorithm. Each research participant preferred the personalized plastic prosthesis over the energy-storing prosthesis and on par with their own foot. These early clinical data suggest a potential avenue to improving amputees' quality of life by providing personalized, plastic prosthetic feet that can be manufactured and sourced at much lower costs than existing products.



## **Improved Daily Comfort and Mobility for Lower-Limb Amputees Using Novel Release-Relock System**

**Joan Sanders, Ph.D.**, University of Washington

Fluctuations of lower limb volume in a prosthesis after an extended time result in user discomfort and fit. These effects negatively impact an individual's ability to perform daily living activities while using the prosthesis. Two commonly used interventions are a prosthetic sock to cushion the socket or an elevated vacuum system, but these techniques are not ideal because they further reduce limb volume and are prone to leaks, respectively. In FY17, the PRORP awarded Dr. Joan Sanders and her team a Clinical Translational Research Award to further develop the novel TARPIN, To Auto-release & Relock a PIN, system. This device uses a custom-set cable length for sitting, operates seamlessly and effortlessly using one hand, and executes release and relock of the socket, each in less than a few seconds. This award led to the development of a mechanism that quickly pulls in the cable tight for donning, and can release the cable for extension during doffing. Further clinical testing verified the effectiveness of this device and led to further improvements of the system. Based on the successful testing of this device, individuals with a lower limb amputation may soon have an option for a prosthetic socket that easily adjusts to accommodate residual limb volume fluctuation and decreases discomfort throughout the day.

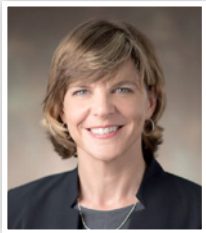




## **Pre-Innervated Muscle Complexes: A New Avenue for Treatment of Volumetric Muscle Loss**

**D. Kacy Cullen, Ph.D., and Suradip Das, Ph.D.,** Corporal Michael J. Crescenz Veterans Affairs Medical Center and the University of Pennsylvania

Volumetric muscle loss from orthopaedic trauma or surgical interventions results in substantial functional deficits in joint range of motion and skeletal muscle strength, which may cause lifelong dysfunction and disability. Current clinical procedures such as muscle grafts and tissue-engineered muscle products often fail due to limited nerve intervention at the muscle site. The current gold standard of treatment for volumetric muscle loss is free functional muscle transfer, but the success of this approach is limited due to donor-site morbidity, extensive operation time, and the necessity for the muscles to remain without nerve attachments for a prolonged period of time. With funding from an FY18 PRORP Applied Research Award, Dr. Cullen and his team used a novel mechanical bioreactor to facilitate nerve growth and develop tissue-engineered muscle to promote functional muscle regeneration following volumetric muscle loss. Specifically, their approach uses a bioreactor with either muscle or myocyte cells grown in combination with nerve cells to help induce muscle stimulation to promote movement. The researchers implanted the cellular scaffolds into a small animal model to evaluate their effect. After three weeks of implantation, Dr. Cullen's group found the addition of nerve cells promoted muscle volume recovery, higher host cellular infiltration, and increased revascularization compared with the control group lacking nerve cells. The team's findings suggest nerve cells significantly increase the functional regeneration of muscle at the site of injury for patients experiencing volumetric muscle loss. Upon future testing, the ability to regenerate lost or damaged tissue could dramatically improve clinical outcomes and long-term recovery of Service Members, Veterans, and civilians impacted by traumatic injury.



## **New Information on Our Understanding of Osteoarthritic Onset**

**Tamara Alliston, Ph.D.,** University of California, San Francisco

Osteocytes, or mature bone cells, can resorb and deposit bone in their surrounding matrix using a process called perilacunar/canalicular remodeling, PLR. With FY13 funds from a PRORP Idea Development Award, Dr. Tamara Alliston and her team investigated the role of PLR and the subchondral bone in the development of osteoarthritis. Based on a comparative analysis of patients' osteoarthritis tissue and tissue free from osteoarthritis, the team identified noticeable changes to subchondral bone, increased mineralization, and misaligned bone matrix fibers in patients with late-stage osteoarthritis. To determine whether the osteocyte bone cells and deregulated PLR are at the root of osteoarthritis onset rather than a consequence of the disease, Dr. Alliston's group deleted the MMP13 gene, which plays a role in the initiation of PLR, in normal osteocyte bone cells in a mouse model. The team found evidence of osteoarthritis within the articular cartilage of the mice. This work implicates for the first time a disruption in normal osteocyte biology as a primary event in the onset of osteoarthritis. The result of Dr. Alliston's work advances the understanding of significant gaps in the knowledge of osteoarthritis mechanisms associated with development of joint disease and could significantly impact advancement of osteoarthritis treatments for both Service Members and the general public who are suffering from chronic joint disease.



## **Cognitive Function and ACL Rehabilitation**

**Dustin R. Grooms, Ph.D., AT, CSCS,** Ohio University

Surgical reconstruction and physical therapy of the anterior cruciate ligament often have high rates of reinjury and long recovery times. Current rehabilitation methods tend to focus on mechanical milestones relating to knee motion and load, but data on the impact of the central nervous system on recovery are limited. Dr. Dustin Grooms received an FY17 PRORP Applied Research Award to quantify brain activity and the effects of cognitive interference in high-risk and anterior cruciate ligament injury-repaired individuals with the goal of developing new rehabilitation strategies. Dr. Grooms and his team's findings from evaluating high-risk individuals suggest elevated brain activity in specific regions is associated with a higher risk of injury. For cognitive interference, the investigators evaluated Reserve Officers' Training Corps members at a simulated shooting range and found adding visual cognitive challenges delayed shot initiation and completion times. From these studies, Dr. Grooms and his team developed tests for return to athletic activity incorporating cognitive-motor interference and found that adding a visual-cognitive challenge improved outcomes. The benefits of environmental and cognitive load demonstrate the importance of cognitive function in physical rehabilitation, which could be used to aid both civilian and military populations going forward.

# FUTURE

The PRORP hosted a stakeholders meeting in September 2021 to identify current critical knowledge and capability gaps in orthopaedic research and care, with the purpose of informing future PRORP research funding and strategic directions. Representatives from non-profit organizations, academia, industry, government institutions, and the public worked together to identify primary and secondary gaps requiring additional attention to advance the field of orthopaedic research. Focus areas included:



Care for Return to Duty  
Within One Year of Injury  
for Service Members



Diagnosis and Acute  
Care of Prehospital  
Musculoskeletal Trauma  
Injuries in Military and  
Civilian Populations



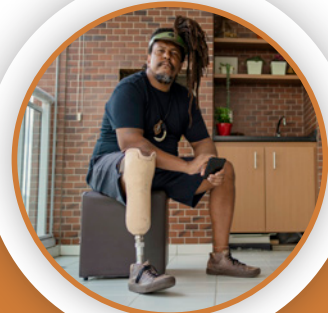
Emerging Areas  
in Preclinical  
Orthopaedic Research



Emerging Areas in  
Clinical Orthopaedic  
Research



Knowledge Gaps  
in Surgical Care for  
Musculoskeletal Combat  
Casualties



Knowledge Gaps  
in Surgical Care for  
Musculoskeletal Non-  
Combat Casualties



Representatives shared broad perspectives on barriers in research and patient outcomes, key knowledge and scientific gaps, and potential approaches for addressing orthopaedic needs. Resources shared during the stakeholders meeting and outcomes of the effort are posted on the CDMRP website.

In addition to the stakeholders meeting, the PRORP coordinates with partners from other federal and non-government funding organizations. Among these varied research funding organizations, the PRORP anticipates it will have the most impact on orthopaedic care by supporting high-risk/high-reward research, multidisciplinary research, and research projects that will move promising findings closer to clinical implementation and/or availability.

Capitalizing on the gaps identified during the stakeholders meeting, consulting with other orthopaedic research funders, and in conjunction with the Programmatic Panel, the PRORP developed an FY23 Strategic Plan. This plan includes funding allocation and award mechanisms planned for the FY23-FY27 PRORP, provided funds are appropriated to the program by Congress. It also reflects the types of research, such as applied or solutions-driven, translational, or clinical research, that the program plans to fund, based on the needs of the field. The PRORP will incorporate these topics and others realized during the program's annual Vision Setting meeting over the next several years provided they remain consistent with congressional direction. Some areas of interest to the PRORP include:

-  Pre-hospital wound management, e.g., tissue preservation, infection management, strategic timing of treatments, and care strategies to prevent secondary injuries and complications.
-  Novel surgical techniques and technologies for enhancing limb restoration.
-  Prevention and treatment of complications following surgical treatment of musculoskeletal non-battle injuries.
-  Novel musculoskeletal imaging capabilities for diagnosis of the underlying cause of orthopaedic injury and the efficacy of interventions measurements.
-  Development of new or leveraging of existing technologies and/or personalized care approaches to augment or aid surgical care, monitor/follow recovery, assess return to activity/duty, or identify early predictors of failure.
-  Development of tissue engineering and supportive structural scaffolds to augment, accelerate, or improve musculoskeletal injury treatments.
-  Development of biologic compounds, implants/devices, combination products, pharmacologic, or non-pharmacologic interventions to improve regeneration of composite tissue, often including muscle, nerve, tendon, and bone.
-  Solutions for traumatic tissue loss, with a focus on healing crushed or severed nerves with successful innervation, significant muscle loss, and protection or restoration of limb and wound vascularity.
-  Interventions to prevent, detect, modulate, or treat infection, acute inflammation, and/or harmful immune response in the context of orthopaedic repair across the continuum of care.
-  Strategies for longitudinal monitoring of musculoskeletal healing and functional recovery.
-  Therapies and techniques to decrease and treat complications and improve outcomes following high-energy extremity trauma.
-  Development of innovative prosthetics, orthotics, and/or robotics to assist with mobility after traumatic injury.

For more information on stakeholders meeting outcomes and the FY23 Strategic Plan, please visit <https://cdmrp.health.mil/prorp/default>

The PRORP released three award mechanisms to help address the identified PRORP research priorities: the **Applied Research Award**, **Clinical Translational Research Award**, and **Clinical Trial Award**.



The **ARA** supports applied research projects focused on advancing optimal treatment and restoration of function for individuals with musculoskeletal injuries sustained during combat- and service-related activities. Although the ARA allows basic and animal research, it is not intended to support fundamental basic research without specific application toward knowledge or tangible products.



The **CTRA** supports translational clinical research that may not yet be ready for a full-scale randomized clinical trial. Funded projects are expected to impact the standard of care for military, Veteran, and all patients who have sustained orthopaedic injuries.



The CTA supports rapid implementation of clinical trials that can have a significant impact on treatment or management of military combat or service-related orthopaedic injuries that impact unit readiness and return to duty/work rates. While the CTRA allows clinical research projects, the **CTA** is restricted to clinical trials only.

The PRORP will evaluate the strategy of supporting these award mechanisms and update as necessary during the program's annual Vision Setting meeting. This is consistent with the program's goal in funding impactful, high-risk/high-reward, and clinically meaningful research. PRORP aims to address the most critical knowledge and capability gaps in orthopaedic research with a focus on clinical implementation for military Service Members and the public.









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