2014 METRC Annual Report

Major Extremity Trauma Research Consortium

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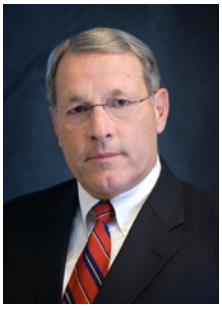
METRC
Major Extremity Trauma Research Consortium



Dear Colleagues and Friends,

We are completing an exceptional year! All but one of our funded studies are in the field and actively enrolling patients. At our present rate of enrollment, we will pass 3,000 enrolled patients before year's end. We just entered the last year of the METRC I Grant and are in great shape with the related studies. The Registry was completed in 25 Centers. The Bioburden Study should complete enrollment by the end of the year. pTOG has increased both in the number of participating centers and in cases enrolled. As of 1 September 2014, we had enrolled 246 patients into the FIXIT trial.

METRC II studies are also reaching potential. We anticipate concluding enrollment in the OUTLET, TCCS and PACS studies by early 2015 and we are continually re-assessing enrollment patterns in PAIN and TAOS.

METRC studies funded through the DoD PRORP and NIH NIAMS are also picking up steam. POvIV, PTOA, Oxygen and STREAM started enrolling this year. ProFIT and VANCO will soon be enrolling their first patients.

Critical to our on-going success is the commitment of the clinical sites to the core mission of the consortium and constant attention to quality assurance and quality improvement. The Coordinating Center continues its efforts at site monitoring, working closely with centers to ensure regulatory compliance and data quality. We have seen significant improvements in site performance across several domains that span the life cycle of our studies, from regulatory review though enrollment and patient follow-up.

By the end of 2014, we will have completed a visit to each core site, providing each Center with an overview of METRC and site performance comparisons. The effort has been very positive. It was great to witness firsthand the enthusiasm of all the people who contribute to the success of METRC.

Our challenges remain the same. We need to indentify, screen and enroll every eligible patient. Once enrolled, we need to focus on 100% follow-up so that we can answer the research questions we believe are critical in making a difference in the lives of our trauma patients, service members and civilians alike.

We look forward to an exciting year as we begin data analysis and report the first of our study results. We want to thank everyone for their overriding commitment to METRC. Collectively, we have been granted an opportunity of historical magnitude. We will work hard in the coming years to make sure we deliver on that opportunity.

Sincerely,
Michael J. Bosse, MD
Ellen J. MacKenzie, PhD

About METRC

Advancing Limb Trauma Care through Research

The Major Extremity Trauma Research Consortium (METRC) was established in September of 2009 with funding from the Department of Defense (DoD). It is comprised of a network of clinical centers and one data coordinating center that work together with the DoD to conduct multi-center clinical research studies relevant to the treatment and outcomes of orthopaedic trauma sustained in the military.

Improving outcomes through collaborative research

The overall goal of the METRC Consortium is to produce the evidence needed to establish treatment guidelines for the optimal care of the wounded warrior and ultimately improve the clinical, functional and quality of life outcomes of both service members and civilians who sustain high-energy trauma to the extremities.

The need for a Consortium dedicated to improving outcomes following major limb trauma is evident. Approximately 55% of all service members injured in OIF/OEF/OND sustain significant extremity trauma. Many are burdened with injuries to multiple limbs. Complex wound management, infection, bone loss, articular surface loss, blast-related extremity heterotopic ossification, segmental nerve loss, complete muscle tendon unit loss and compartment syndrome have been identified as critical challenges in caring for our wounded warriors. These challenges are only compounded by the needs in the post-acute and rehabilitation phases of recovery. Rigorous clinical research is sorely needed to address these challenges. This research must rely on a multi-disciplinary approach that combines the clinical insights of the military and civilian orthopaedic surgeons and rehabilitation specialists, the research acumen of a world renowned clinical research center and the high volumes of patients with severe injuries that are treated at major Level I trauma centers and the military treatment facilities (MTFs). METRC is designed to meet these needs.

Anchored by a Data Coordinating Center at the Johns Hopkins Bloomberg School of Public Health and its Center for Injury Research and Policy, the Consortium includes 22 core Level I civilian trauma centers and 4 core MTFs – with the ability to expand patient recruitment to more than 30 additional satellite trauma centers. The Consortium works collaboratively with the DoD to:

1. *Continuously identify the most critical issues that challenge recovery from major orthopaedic trauma;*
2. *Develop and sustain a research infrastructure to support the conduct of multi-center research studies aimed at the rigorous evaluation of current standards of orthopaedic care;*
3. *Partner with basic scientists and engineers to facilitate the translation of new and emerging technologies into clinical practice;*
4. *Mentor young orthopaedic trauma surgeons and rehabilitation specialists in the design and conduct of clinical trials;*
5. *Contribute to the science of fracture and soft tissue repair;*
6. *Contribute to the science of conducting clinical trials in a challenging patient population and treatment environment.*

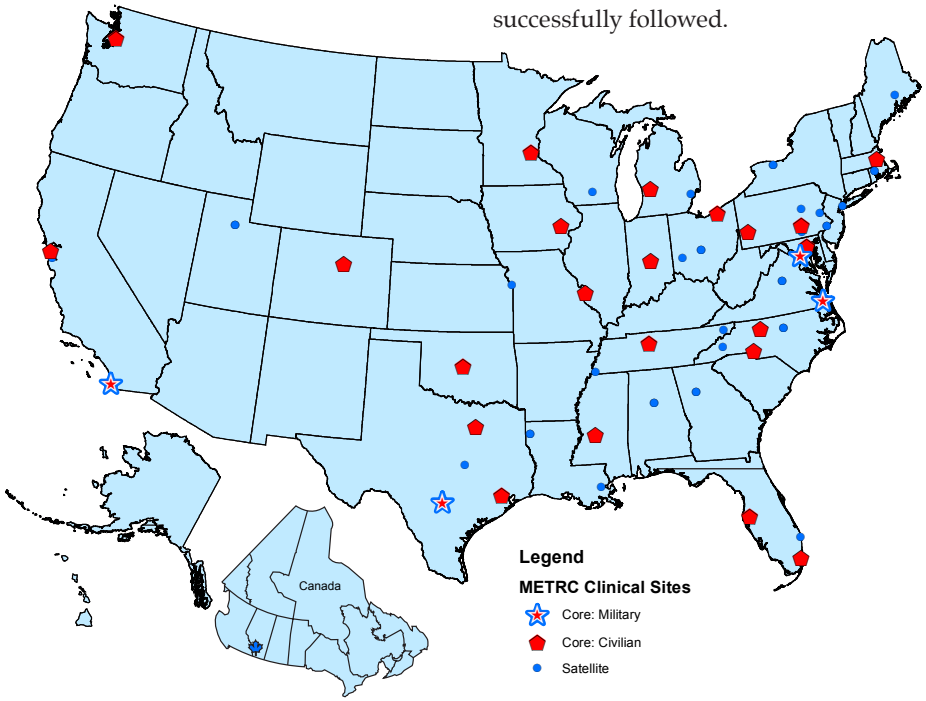
METRC is committed to conducting high quality clinical research that will make a difference in the lives of those who sustain major orthopaedic trauma. It does so by establishing a clinical research network that is dynamic and responsive to new clinical challenges or the emergence of new, promising novel therapies. The success of the Consortium depends on the identification of critical topics, the design of clinical trials that are sensitive to the realities of surgical patient research, rapid and high volume recruitment to those studies and excellent post-treatment follow-up. It also depends on the responsiveness of the network to specific centers and studies that are not meeting expectations and its ability to re-allocate resources and re-focus priorities accordingly.

Core funding for METRC is provided through the Orthopaedic Extremity Trauma Research Program (OETRP) (Award # W81XWH-09-2-0108) and a cooperative agreement with the DoD Peer Reviewed Orthopaedic Research Program (PRORP) of the Congressionally Directed Medical Research Program (CDMRP) (Award # W81XWH-10-2-0090).

The backbone of the Consortium consists of a dedicated group of core and satellite clinical centers located throughout the United States.

The **Core Clinical Centers** include 22 civilian trauma centers and the four military hospitals receiving the majority of major casualties, including Walter Reed National Military Medical Center (WRNMMC), San Antonio Military Medical Center (SAMMC), the Naval Medical Center in San Diego (NMCSD) and the Naval Medical Center in Portsmouth (NMCP). The civilian core centers are large, level I trauma centers with leading orthopaedic trauma programs and established research infrastructures. The core clinical centers are provided with resources to support METRC activities and participate in most trials sponsored by the Consortium. These centers were chosen on the basis of their volume of major extremity trauma cases, commitment to research, experience in participating in large multi-center studies, and academic qualifications.

The **Satellite Clinical Centers** are civilian trauma centers with an established orthopaedic trauma program. They are invited to participate in individual METRC studies to ensure adequate numbers and appropriate mix of patients. Their participation is supported by a start-up payment as well as payments provided for each patient screened, enrolled and successfully followed.

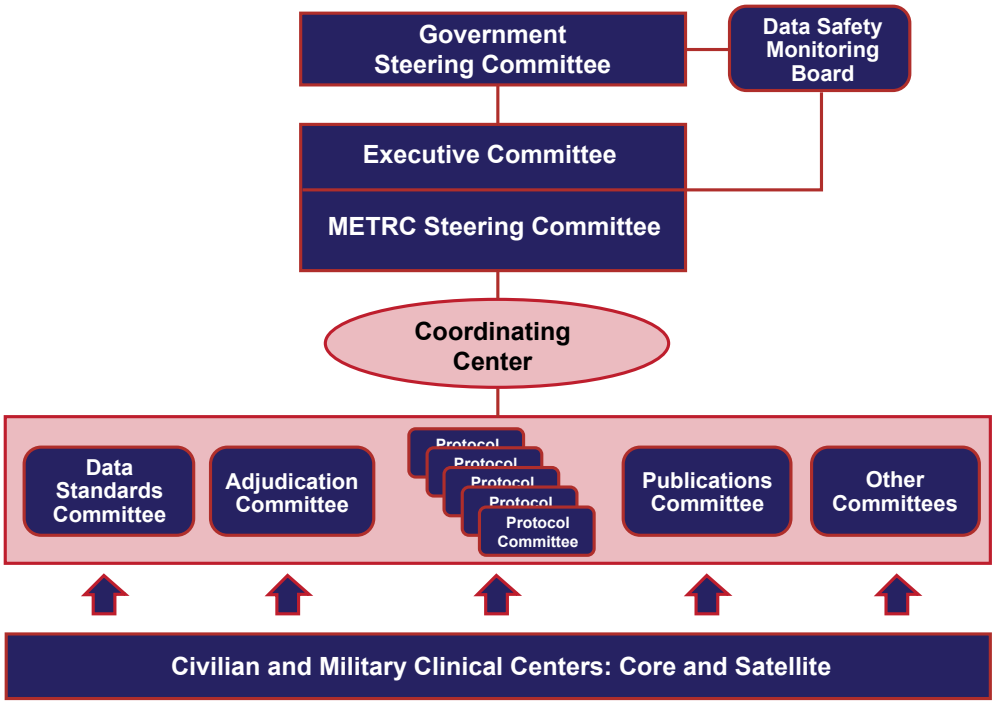


A current list of both core and satellite centers is provided in Appendix A at the end of this report.

The primary decision-making body of the Major Extremity Trauma Research Consortium (METRC) is the METRC Steering Committee, which is a representative body of the investigators and the U.S. Military. The Steering Committee provides ongoing oversight in planning and conducting each study sponsored by the Consortium and approves all study protocols. The Steering Committee meets monthly by WebEx-facilitated conference calls and in-person at least twice each year.

The Executive Committee serves as the agent of the Steering Committee in carrying out the day-to-day administrative responsibilities of the Consortium and Consortium-sponsored studies. The Consortium is supported by a network of Standing Committees, including: (1) Publications and Presentations; (2) Data Standards; (3) Clinical Outcomes Adjudication; and (4) Study-Specific Protocol Committees.

The Military Steering Committee was established by the DoD to (1) review progress of METRC; (2) provide advice and guidance on scientific and military relevance; (3) coordinate proposed projects with other military relevant orthopaedic trauma initiatives; (4) provide approval on all proposed Consortium studies prior to implementation; and (5) recommend areas of future study to the Consortium.



The Coordinating Center for METRC is located at the Johns Hopkins Bloomberg School of Public Health. The Coordinating Center works closely with the METRC Steering Committee to ensure that study protocols are appropriately designed, executed and analyzed. The Center is organized around several core functions: (1) Protocol Development and Implementation; (2) Informatics; (3) Data Management and Analysis; (4) CRF Development and Maintenance; (5) Monitoring, Training and Quality Improvement; and (6) Administration and Regulatory Oversight. Resources of the Johns Hopkins Biostatistics Center are used to further support the data management and analysis activities of the Center. A list of key personnel of the Coordinating Center is available in Appendix B.

JOHNS HOPKINS BLOOMBERG SCHOOL of PUBLIC HEALTH

The METRC Data Safety Monitoring Board (DSMB):

A DSMB was established for METRC and acts in an advisory capacity to the DoD and the METRC Steering Committee to monitor patient safety and evaluate the efficacy of the interventions under study. Dr. Marc Swiontkowski of the University of Minnesota is chair of the DSMB and serves as Medical Monitor. Other members of the board are listed here. The DSMB meets at least two times a year and more frequently as necessary.

METRC Data Safety Monitoring Board

Marc Swiontkowski, MD (CHAIR)
Department of Orthopaedics
University of Minnesota

Baruch Brody, PhD
Andrew Mellon Professor of Humanities
Department of Philosophy
Rice University

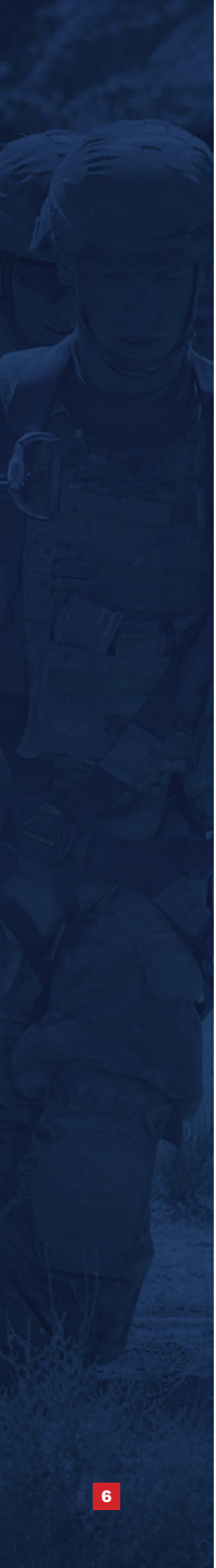
Hans Kreder, MD, MPH
Department of Orthopaedics
Sunnybrook Health Sciences Centre

Stephen Walter, PhD
Department of Clinical Epidemiology & Biostatistics
McMaster University

Capt. Christopher Ayres USMC (Ret.)
OIF Combat Wounded
Hewlett-Packard Enterprise Services

Thomas Decoster, MD
Department of Orthopaedics
University of New Mexico Medical Center

Eli Powell, MD Col (Ret.)
Alaska Orthopaedic Surgery and Sports Medicine
Anchorage, AK



Ensuring Quality Research

METRC is committed to efficient and high quality research design and data collection. To this end, procedures have been put in place to document Consortium-wide and study-specific policies and procedures, facilitate communication across the Consortium, standardize approaches to data collection and support rigorous continuous data quality assurance.

Policies and Standard Operating Procedures (SOPs):

The policies governing METRC were developed in 2010 and are re-visited on a regular basis and amended as appropriate. They include polices on:

- Governance
- Approval and Initiation of Studies
- Conflict of Interest and Commitment
- Publications and Presentations
- Data Standards and Data Collection

In an effort to standardize the processes and procedures utilized by the Consortium, we have developed several Standard Operating Procedures (SOPs) and compiled them into a Manual of Operations (MOP) for METRC. These SOPs are distributed to all participating centers and made available on the website. Amendments to these SOPs are made as necessary.

Standard Operating Procedures (SOPs)

1. **METRC Overview and Policies**
2. **METRC Communications**
3. **Data Safety and Monitoring Board**
4. **Study Initiation**
5. **IRB Submission and Study Documentation**
6. **Clinical Site Certification**
7. **Patient Screening**
8. **Reporting Requirements**
9. **METRC Data Management**
10. **Patient Payments**
11. **Patient Follow-up**
12. **Case Report Form Management**
13. **HIPAA Compliance**
14. **Medical Care Costs Data**
15. **Data Quality Assurance**
16. **Clinical Site Monitoring**
17. **Research Coordinator Advisory Committee**
18. **Data Sharing**

Data Standards:

METRC has developed a Data Standards and Data Collection Policy that governs the development of case report forms (CRFs) and strategies for data collection. Core data elements are collected uniformly across all studies except in specific studies of limited scope. Collecting core data across studies allows us to combine and analyze outcomes across studies, compare study populations, conduct METRC-wide secondary data analyses and serve as a starting point for CRF development for any given study. The twelve core domains for data collection are summarized here.

In addition to developing the core data elements to be collected across all studies, we have developed standard procedures for collecting data common to many studies. Standards have been developed for measuring infection, fracture healing and functional performance.

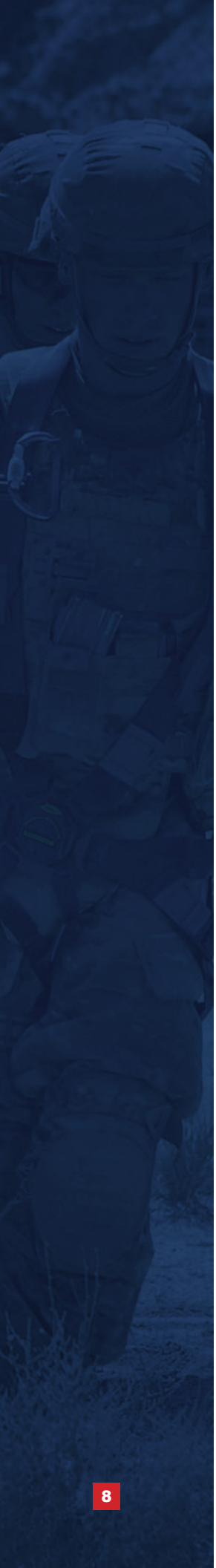
REDCap
Research Electonic Data Capture

The centerpiece of the METRC data management infrastructure is the Research Electronic Data Capture (REDCap) system hosted at the Coordinating Center. REDCap is a state of the art, metadata driven application for distributed data collection and data management in clinical studies. The REDCap data management functionality allows for a secure, web-based data entry system that uses a web browser to access an internet-connected database server.

Standard Data Collection across all METRC studies

1. **Patient Demographics**
2. **Socioeconomic Status**
3. **Usual Major Activity**
4. **Health Insurance**
5. **Psychosocial Predictors of Outcome**
6. **Smoking History**
7. **Height and Weight**
8. **Co-morbidities**
9. **Pre-Injury Health Status**
10. **General Injury Characteristics**
11. **Mechanism and Type of Injury**
12. **Functional Outcomes**

The system permits both the Coordinating Center and clinical sites to have access to data as soon as they are entered, allowing for near-real-time recruitment reports and increased data entry availability and convenience for the clinical sites. The primary functions of the data system include the following features: registration of all candidates for the trial; randomization to study arms; entry of all study data forms; inventory, management, and editing of study data; maintenance of full audit trails of all data entry and editing; and generation of real time performance reports. The REDCap data entry system also includes extensive data validation functionalities, including field level validation.



Continuous Quality Improvement:

Critical to the success of any multi-center trial is a robust data quality assurance and improvement plan. Quality assurance involves development and maintenance of proper attitudes among all investigators and research staff as well as the use of study designs that protect the results from bias. Beyond these strategies, assurances depend on procedures used for training, data collection and analysis. Paramount among these is the training and certification of study personnel involved in data collection, and the maintenance of those certifications throughout the trial. Additionally, data audits are performed to ensure collection of quality data. Monthly and Quarterly Reports are generated to monitor site performance and overall progress on each study:

- **Study and Site Specific Monthly Reports** summarize the numbers of patients screened and enrolled by month and track patient follow-up and data completeness by study ID. Sites are required to respond to errors within two weeks.
- **Study Specific Quarterly Reports** include updates on overall and site specific recruitment and enrollment and compare actual enrollment against projected enrollment. These reports are reviewed by the Study Protocol Committees and actions taken as necessary to improve the rate of enrollment and data quality.
- **DSMB Reports** are generated at least two times each year and more often as requested by the DSMB. These reports consist of both open and closed reports and are used as a basis for discussion at the DSMB meetings.

Also important to assuring quality are formal on-site monitoring visits of METRC sites that are actively recruiting patients into one or more studies.

In addition to the monthly and quarterly reports described above, METRC produces site specific performance reports on a semi-annual basis that are used to highlight areas of excellence, establish benchmarks for success and look critically at areas in need of improvement. These reports are also used to assist METRC leadership in making decisions regarding the alignment of study resources with the level of site activity. Site performance is evaluated in five domains that span the implementation life cycle of METRC studies, from initial regulatory review and approval through study follow-up and data quality assurance efforts. An indicator of volume which is based on number of participants enrolled and followed is also used in evaluating the overall contribution of each site. Domain specific and overall performance scores are produced for each center and graphically displayed showing center performance compared to internally set benchmarks and to the average performance of all core sites.

As of September 1, 2014 METRC has prospectively enrolled 2,355 patients into 11 studies. Our top twelve enrolling sites (as of September 1, 2014) are listed below:

Carolinas Medical Center
Principal Investigator & Chair of the METRC Consortium: Michael J. Bosse, MD

University of Maryland R Adams Cowley Shock Trauma Center
Principal Investigator & Co-Chair of the METRC Consortium: Andrew N. Pollak, MD

UT Health: The University of Texas Health Science Center at Houston
Principal Investigator: Joshua Gary, MD

Vanderbilt University Medical Center
Principal Investigator: William T. Obremskey, MD, MPH

Washington University Methodist Hospital
Principal Investigator: Todd McKinley, MD

MetroHealth Medical Center
Principal Investigator: Heather A. Vallier, MD

Wake Forest University Baptist Medical Center
Principal Investigator: Eben Carroll, MD

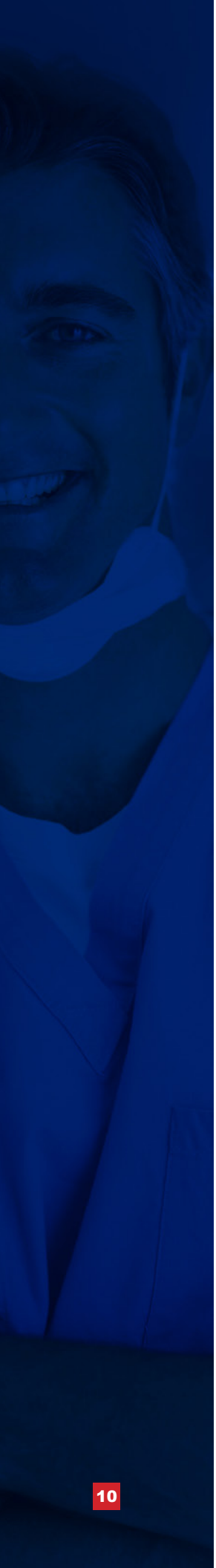
Florida Orthopaedic Institute / Tampa General & St. Joseph's Hospitals
Principal Investigator: Roy W. Sanders, MD

Hennepin County Medical Center & Regions Hospital
Principal Investigators: Andrew H. Schmidt, MD & Paul Lafferty, MD

Orthopaedic Associates of Michigan / Spectrum Health
Principal Investigator: Clifford B. Jones, MD

University of Mississippi Medical Center
Principal Investigator: George Russell, MD

University of Miami Ryder Trauma Center
Principal Investigator: Gregory A. Zych, DO



The METRC Registry

In 2010, a 'start-up' registry was established to assist the Consortium in determining the feasibility of future studies that could address critical research questions with adequate power. The registry is also used to monitor enrollment of current studies by estimating the expected number of patients to be screened for any one study and then comparing the expected numbers to the observed numbers screened.

All core centers were asked to implement and maintain the registry for at least 365 consecutive days. The registry contains a limited set of data on patients between the ages of 18 and 84 who were admitted with fractures requiring surgery of the upper or lower extremity, pelvis or acetabulum, and foot (calcaneus, talus or crush injuries only). Excluded from the registry are hip fractures in patients 60 years or older and fractures to the wrist, hand, ankle, clavicle, patella, and the foot other than calcaneus/talus/crush.

The table to the right provides annual estimates of the number of 'registry' fractures treated per site and across the 25 core sites who contributed to the registry. The 25 sites together treat a total of 15,316 'registry' type fractures each year (including 230 traumatic amputations). Over three quarters (79%) of all fractures are to the lower extremity. Nearly one quarter (22%) of all fractures are open and of the open fractures, 48% are Gustilo type III (33 % IIIA, 12% IIIB and 4% IIIC).

An estimated 403 amputations (traumatic and surgical) are registered annually across the 25 core sites (44 to the upper limbs and 359 to the lower limbs).

Overall, the registry has underscored the advantages of combining data on the population of injured service members with data from civilian orthopaedic trauma centers to conduct the research necessary to improve the outcomes of both service members and civilians who sustain high energy extremity trauma. For instance, while rates of rare injuries critical to studies on the treatment of major segmental bone loss are higher in military centers (15 %) compared to civilian centers (6%), the absolute numbers at combined civilian centers (n=187) are much higher than at the military centers alone (n=36). Similarly, while severe contamination embedded in bone that is characteristic of war wounds presents at higher rates in military centers (38% vs. 11%), the absolute numbers again favor collaboration with high volume civilian centers (n=94 vs. n=352). Overall, 239 open extremity fractures presented to military centers during the study period whereas civilian centers saw 3,033 open extremity fractures during the same time period.

Nerve Injuries Associated with Major Limb Trauma

While nerve injuries associated with upper and lower extremity trauma can have devastating consequences, little is known about their overall incidence and treatment. A subset of 15 Core METRC Centers collaborated to extend the METRC registry to facilitate the collection of data on 353 major nerve injuries in the upper (n=250) and lower (n=103) extremities. Upper limb zones of injury included the brachial plexus (10%), proximal, mid and distal humerus/elbow (3%, 15%, and 23%, respectively), forearm (32%), and wrist (17%). Lower extremity zones of injury included the lumbar plexus (2%), hip/thigh (17%), knee (19%) and below the knee (53%). Forty percent of upper extremity nerve injuries and 72% of lower extremity nerve injuries were associated with a fracture. Two thirds of the injuries treated non-operatively. The majority that underwent repair or reconstruction were done so with nerve tubes (followed by nerve wraps, allograft, autograft, and nerve transfers). The registry data highlight a lack of standardization in care of extremity nerve injuries and demonstrate the potential to gather sufficient numbers for conducting prospective studies to evaluate variation in care and outcomes following repair and reconstruction.

Annual Number of Registry Fractures by Upper and Lower Limb and OTA Code

(based on data as of August 28, 2014)

	Annual Number of Registry Fractures	
	Average Per Site	**Total for 25 Sites**
All Upper Limb Fractures	**130**	**3256**
Traumatic Amputations	1	29
Closed Fractures	95	2369
Open Fractures	34	858
Gustilo Type I or II	22	562
Gustilo Type III	12	296
Humerus	**65**	**1626**
11 A,B,C (% open)	24	605 (6%)
12 A,B,C (% open)	21	526 (22%)
13 A,B,C (% open)	20	495 (36%)
Radius/Ulna	**68**	**1702**
21 A,B,C (% open)	30	745 (28%)
22 A,B,C (% open)	38	957 (35%)
All Lower Limb Fractures	**482**	**12060**
Traumatic Amputations	8	201
Closed Fractures	371	9286
Open Fractures	103	2573
Gustilo Type I or II	49	1223
Gustilo Type III	54	1350
Pelvis /Acetabulum	**87**	**2190**
61 A,B,C (% open)	42	1055 (6%)
62 A,B,C (% open)	45	1135 (2%)
Femur	**156**	**3909**
31 A,B,C (% open)	46	1447 (4%)
32 A,B,C (% open)	77	1936 (20%)
33 A,B,C (% open)	33	826 (30%)
Tibia	**204**	**5086**
41 A,B,C (% open)	66	1644 (12%)
42 A,B,C (% open)	81	2024 (50%)
43 A,B,C (% open)	57	1418 (31%)
Foot	**44**	**1095**
81 A,B,C (% open)	14	355 (26%)
82 A,B,C (% open)	27	675 (18%)
89 A,B,C (% open)	3	65 (57%)

Ongoing Research of the Consortium

Research cores have been established to facilitate the development of research priorities and identification of studies (see box). These are the priorities used by the METRC and Military Steering Committees in selecting and approving specific studies to be conducted by the Consortium. Each decision is made after careful consideration of the importance and relevance of the research question, integrity of the proposed study design, feasibility, and availability of funding (either through the core funds of the Consortium or through outside funding).

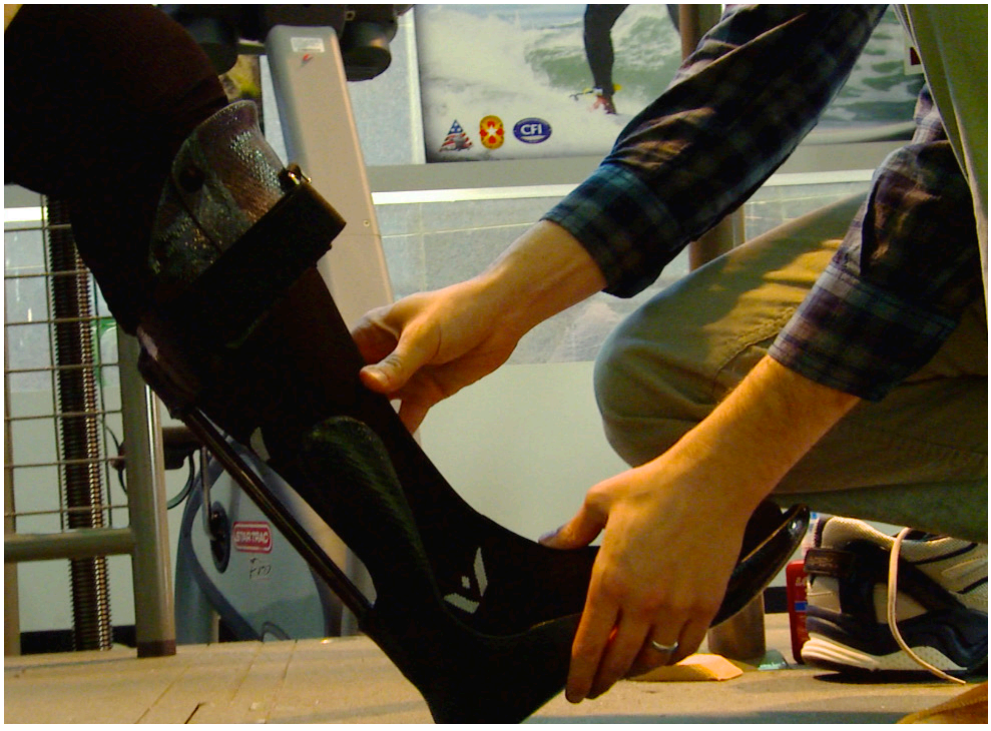
METRC encourages collaboration with industry in the evaluation of proprietary investigational agents under guidelines set forth by the Consortium. These guidelines, established to maintain the independence and scientific integrity of the Consortium, pertain to protocol development, data access, publication review and intellectual property. In particular, all industry sponsored studies must involve METRC investigators in protocol development and the final study protocol must be approved by the METRC Steering Committee. Collection and analysis of the data remain the responsibility of METRC and its Coordinating Center, independent of industry involvement.

Core Research Areas

- **Bone Defect Reconstruction and Fracture Healing**
- **Prevention and Treatment of Acute and Chronic Infections**
- **Diagnosis and Treatment of Compartment Syndrome**
- **Wound Care and Closure**
- **Prevention and Treatment of Post-Traumatic Osteoarthritis (PTOA)**
- **Limb Salvage and Amputation Outcomes**
- **Long-term and Rehabilitation Outcomes**

METRC is currently funded to conduct 15 studies that address six of the seven core areas of research.

These studies are listed to the right, organized by the source of funding.



DoD OETRP
(core funding for METRC I)

- **pTOG:** An RCT comparing rhBMP-2 vs. autograft for critical size tibial defects
- **FIXIT:** An RCT comparing ring external fixation vs. locked IM nail as the definitive stabilization of Grade IIIB tibia fractures
- **BIOBURDEN:** Assessment of severe extremity wound bioburden at the time of definitive wound closure or coverage: correlation with subsequent post-closure deep wound infection

DoD CDMRP
(core funding for METRC II)

- **OUTLET:** Outcomes following severe distal tibia, ankle and/or foot trauma: comparison of limb salvage vs. transtibial amputation
- **PACS:** Predicting acute compartment syndrome using optimized clinical assessment, continuous pressure monitoring, and continuous tissue oximetry
- **PAIN:** An RCT comparing efficacy of standard pain management vs. standard care combined with use of perioperative pregabalin or ketorolac in the treatment of severe lower limb fractures
- **TAOS:** An RCT comparing transtibial amputation with and without a tibia-fibula synostosis
- **TCCS:** Using a collaborative care model to improve quality of life following extremity trauma

DoD PRORP Clinical Trial Awards

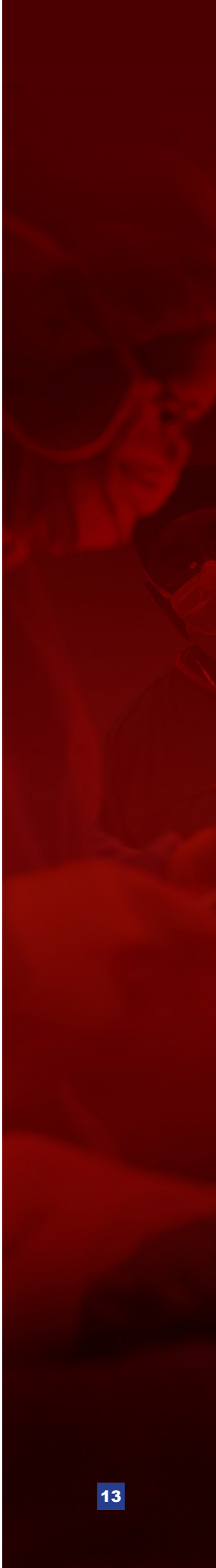
- **VANCO:** An RCT evaluating local antibiotic therapy to reduce infection after operative treatment of fractures at high risk of infection (primary award to University of Maryland)
- **OXYGEN:** An RCT evaluating supplemental perioperative oxygen to reduce surgical site infection after high-energy fracture surgery (primary award to University of Maryland)
- **POvIV:** An RCT to assess oral vs. intravenous antibiotics for treatment of early post-op infection after plate fixation of extremity fractures (primary award to Vanderbilt University)
- **proFIT:** Prosthetic Fit Assessment in Transtibial Amputees Secondary to Trauma (primary award to University of California, San Francisco)

NIH National Institute of Arthritis, Musculoskeletal and Skin Disorders (NIAMS)

- **PTOA:** Multi-center investigation of the mechanical determinants of post-traumatic osteoarthritis (primary award to University of Iowa)
- **STREAM:** Reliability and Responsiveness of PROMIS tools in Orthopaedic Trauma Patients (primary award to Johns Hopkins University)

DoD USMRMC TATRC

- **PRIORITI-MTF:** Patient response to an integrated orthotic and rehabilitation initiative for lower extremity injuries in the military (primary award to Johns Hopkins University)



Each study currently funded by METRC is described in a one page brief that follows. For more information, visit the METRC website www.metrc.org

Assessment of Severe Extremity Wound Bioburden at the Time of Definitive Wound Closure or Coverage: Correlation with Subsequent Post-Closure Deep Wound Infection

The BIOBURDEN Study

Sponsored by: DoD OETRP
Award Number: W8XWH-09-2-0108 (METRC I)
PI/Protocol Chair: Michael Bosse, MD

The primary objective of this study is to characterize the contemporary extremity wound "bioburden" at the time of definitive wound coverage/ closure of severe extremity military and civilian wounds. Routine tissue samples collected as part of standard care will be analyzed employing both standard tissue culture microbiology and modern polymerase chain reaction (PCR) technologies. The secondary objectives of the study are to determine 1) the correlation of the identified wound pathogens at the time of wound closure/ coverage with subsequent deep wound infections; 2) the correlation of the PCR results with those obtained from standard hospital microbiology; and 3) the efficacy, if any, of antibiotics used in the care of the wound.

There are 40 trauma centers participating in this study (39 are certified)

- 1215 patients have been screened for eligibility and of these, 693 (57%) were eligible at time of consent.
- 547 (78% of eligible) were consented and enrolled into the study.
- 224 patients have completed the study.
- We have now reached 91% of our total enrollment.

Study design: Multi-center, prospective cohort study.

Study duration: 3.5 years (2 year enrollment period, 1 year patient follow up and 6 month data analysis period). Participants are followed for one year after injury.

Sample size: 600 participants.

Number of study centers: 40 core and satellite centers.

Principal Inclusion criteria: All open Type III tibia fractures (plateau, shaft and pilon) requiring a second procedure following fixation, or traumatic transtibial amputations requiring delayed primary closure, skin grafting and/ or flap coverage.

Protocol committee: M Bosse, MD, LCDR J Carney, MD, G Ehrlich, PhD, LCDR J Forsberg, MD, T Miclau MD, LTC C Murray, MD, A Pollak, MD, G Russell, MD, R Seymour, PhD, CDR J Toledano, MD, J Wenke, PhD, M Zadnik Newell, ScD, MEd, OTR/L
From the Coordinating Center: R Castillo, PhD, E MacKenzie, PhD, G deLissovoy, PhD, D Scharfstein, ScD, A Carlini, MS, M Zadnik Newell, ScD, MEd, OTR/L.

A Prospective Randomized Trial to Assess Fixation Strategies for Severe Open Tibia Fractures: Modern Ring External Fixators vs. Internal Fixation

The FIXIT Study

Sponsored by: DoD OETRP
Award Number: W8XWH-09-2-0108 (METRC I)
PI/Protocol Chair: Robert O'Toole, MD

The primary objective of this study is to compare outcomes for patients with severe open tibia shaft or metaphyseal fractures with or without a bone defect of any size randomized to treatment with a modern ring external fixator versus standard internal fixation techniques. This study was initially designed to assess 12 month outcomes. Primary outcomes include rate of re-hospitalization for major limb complications, infection, fracture healing, limb function and pain. Secondary objectives are to: 1) determine the percentage of Gustilo IIIB open tibia shaft fractures that can be treated successfully (i.e. without amputation) without a soft tissue flap secondary to the use of ring external fixators; 2) compare the one year treatment costs associated with internal vs. external fixation; and 3) compare patient reported satisfaction with fixation method and overall treatment between the two groups. In early 2014, the protocol was modified to extend follow-up for an additional year.

There are 31 trauma centers participating in this study (27 are certified)

- 561 patients have been screened for eligibility and of these, 285 (50%) were eligible at time of consent.
- 143 (50% of eligible) were consented and enrolled in the RCT; 103 (36% of eligible) were consented and enrolled in the observational study.
- We have now reached 45% of our total enrollment in the RCT.
- 111 patients have completed the 12 month study visit.

Study design: Multicenter, prospective phase III randomized clinical trial. Patients who refuse randomization will be eligible to enroll in a prospective cohort study.

Study duration: 72 months (6 month planning period, 36 month enrollment period, 24 month patient follow-up, and 6 month data and analysis and writing). Participants will be followed for 24 months after injury.

Sample size: 312 participants in randomized study (156 per arm) and 312 in observational study.

Number of study centers: 31 core and satellite centers.

Principal Inclusion criteria: All Gustilo Type IIIB and selected Gustilo Type IIIA diaphyseal or metaphyseal tibia fractures.

Protocol committee: R O'Toole, MD, M Bosse, MD, R Crichlow, MD, W Gordon MD, LTC J Hsu, MD, C Jones, MD, JS Reid, MD, J Sontich, MD, E Carroll, MD, J Gary, MD, J Hutson, MD, A Jahangir, MD, S Quinnan, MD, D Sietsema, PhD, M Fuerst.
From the Coordinating Center: E MacKenzie PhD, R Castillo PhD, G deLissovoy, PhD, D Scharfstein ScD, A Carlini, MS, L Reider, MHS, PhD; J Luly, MS; R Kirk, BS

rhBMP-2 vs. Autograft for Critical Size Tibial Defects: A Multicenter, Randomized Trial

The pTOG Study

Sponsored by: DoD OETRP
Award Number: W8XWH-09-2-0108 (METRC I)
Co-PIs/Protocol Co-Chairs: Lisa Cannada, MD & Paul Tornetta, III MD

The primary objective of this study is to compare rate of fracture healing among patients that have a tibia shaft fracture with a critical size bone defect randomized to treatment with recombinant human bone morphogenetic protein (rhBMP-2/ACS) versus autogenous iliac crest bone graft (ICBG). rhBMP-2 is currently approved for use within the first 14 days in open tibia fractures treated with an intramedullary nail and is commercially available (Medtronic Sofamer Danek, Memphis TN). The FDA has granted an Investigational Device Exemption (IDE) for use of rhBMP-2 in this study. Secondary objectives are to 1) compare rates of infection and functional status between groups; and 2) compare one year medical cost for patients receiving a bone graft randomized to treatment with rhBMP-2 versus ICBG.

There are 16 trauma centers participating in this study (14 are certified)

- 766 patients have been screened for eligibility and of these, 33 (4%) were eligible at time of consent.
- 21 (63% of eligible) were consented and enrolled into the study.
- We have now reached 42% of our total enrollment.
- 7 patients have completed the study.

Study design: Multicenter, prospective phase III randomized clinical trial.

Study duration: 36 months (18 month enrollment period, 12 month patient follow-up, and 6 month data analysis period). Participants will be followed for 12 months after bone graft treatment.

Sample size: 50 participants (25 per treatment group).

Number of study centers: 16 core centers.

Principal Inclusion criteria: Open diaphyseal tibia fractures with a circumferential bone defect of at least one centimeter in length compromising at least 50% of the circumference of the bone treated with an intramedullary nail.

Protocol Committee: L Cannada, MD, P Tornetta, III MD, M Bosse, MD, D Hak, MD, D Stinner, MD, C Jones, MD, S Morshed, MD, W Obremskey, MD, D Teague, MD, R Firoozabadi, MD, C Sagi, MD, H Vallier, MD, A Schmidt, MD, G Zych, MD, J Marsh.
From the Coordinating Center: E MacKenzie, PhD, R Castillo, PhD, G deLissovoy, PhD, D Scharfstein, ScD, Y Weng, MS, L Reider, MHS, PhD, S Collins, MS

A Retrospective Study of the Treatment of Long Bone Defects

The Retro Defect Study

Sponsored by: DoD OETRP
Award Number: W8XWH-09-2-0108 (METRC I)
PI/Protocol Chair: William Obremskey, MD

The primary objective of this study is to characterize the methods of treatment currently being used to repair segmental defects > 1 cm with at least 50% cortical bone loss resulting from an open long bone fracture and to describe the outcomes and incidence of major complications associated with existing treatment methods. The secondary objective is to examine the relationships between treatment modality, union and re-hospitalization for a defined set of complications including amputation (at or proximal to the defect), infection (superficial or deep), flap failure, non-union, mal-union, loss of reduction, or hardware failure. This investigation will provide background data where there is otherwise a knowledge gap due to the relatively low numbers of patients treated with segmental long bone defects at individual institutions.

There are 20 trauma centers participating in this study (20 are certified)

- 1182 records were screened, of which 784 were eligible.
- Data analysis continues.

Study design: Retrospective, multicenter cohort design.

Study duration: 1 year (3 month planning, 6 month accrual, 3 month analysis and writing).

Sample size: 1000 participants.

Number of study centers: 20 core centers.

Principal Inclusion criteria: Long bone fractures (diaphyseal or metaphyseal fracture of either the tibia, femur or humerus) with a circumferential bone defect greater than one centimeter in length with at least 50% cortical loss treated with stable internal or external fixator.

Protocol committee: W Obremskey, MD, M Bosse, MD, L Cannada, MD, C Jones, MD, S Morshed, MD, R O'Toole, MD, D Stinner, MD, P Tornetta, MD. From the Coordinating Center: R Castillo, PhD, E MacKenzie, PhD, D Scharfstein ScD, T Taylor, MPH, J Luly, MS, K Frey RN, MPH

Outcomes Following Severe Distal Tibia, Ankle and/or Foot Trauma: Comparison of Limb Salvage vs. Transtibial Amputation Protocol

The OUTLET Study

Sponsored by: DoD CDMRP PRORP
Award Number: W8XWH-10-2-0090 (METRC II)
PI/Protocol Chair: Michael Bosse, MD

The primary objective of this study is to compare 18 month functional outcomes and health related quality of life (HRQoL) among patients undergoing salvage versus amputation following severe distal tibia, ankle and/or foot injuries with major soft tissue, bone and/or ankle articular surface loss. Secondary objectives are to 1) compare 18 month assessments of physical impairment using objective performance measures of agility, strength/power, speed and balance; and 2) compare levels of participation that will be evaluated by rate and time to return to major usual activity and participation in light, moderate or vigorous recreational or sports activities for patients treated with salvage versus amputation.

There are 35 trauma centers participating in this study (33 are certified)

- 843 patients have been screened for eligibility and of these, 482 (57%) were eligible at time of consent.
- 386 (80% of eligible) were consented and enrolled into the study.
- We have now reached 87% of our total enrollment.
- 16 patients have completed the studythe study.

Study design: Multi-center, prospective longitudinal observational study.

Study duration: 51 months (30 month enrollment period, 18 month patient follow up and 3 month data analysis period). Participants will be followed for 18 months after injury.

Sample size: 464 participants.

Number of study centers: 35 core and satellite centers.

Principal Inclusion criteria: Patients with either (1) Gustilo type III distal tibia and foot or ankle fractures with fracture pattern consistent with one of OTA codes: 43B1.3, 43B2-B3, 43C, 44B, 44C, 81B2-B3, 82B, and 82C; (2) open or closed industrial foot crush injuries; or (3) open or closed foot blast injuries.

Protocol committee: M Bosse, MD, L Cannada, MD, W Gordon MD, C Jones, MD, G Klute, PhD, T Miclau, MD, S Morshed, MD, W Racette CPO, R Firoozabadi, MD, R Seymour, PhD, B Steverson RN, MHA, CCRP, R Teasdall, MD, CDR, J Toledano, M.D, J Wenke, PhD, K Archer-Swygert, PhD, DPT.
From the Coordinating Center: E MacKenzie PhD, R Castillo, PhD, G deLissovoy, PhD, D Scharfstein, ScD, J Luly, MS, L Reider, MHS, PhD, R Kirk, BS

Comparison of Transtibial Amputation with and without a Tibia-Fibula Synostosis

The TAOS Study

Sponsored by: DoD CDMRP PRORP
Award Number: W8XWH-10-2-0090 (METRC II)
Principal Investigator/Protocol Chair: Michael Bosse, MD

The primary objective of this study is to compare levels of impairment and functional outcomes for patients undergoing a transtibial amputation and randomized to receive an end-bearing tibia-fibula synostosis (Ertl procedure) versus a standard posterior flap procedure (Burgess procedure). Secondary objectives are to 1) compare the fit and the alignment of the prosthesis together with levels of comfort and satisfaction between treatment groups; and 2) compare rates of re-hospitalizations for complications, resource utilization, and overall treatment costs for patients undergoing a below the knee amputation who are randomized to receive an end-bearing tibia-fibula synostosis versus a standard posterior flap procedure.

There are 23 trauma centers participating in this study (21 are certified)

- 62 patients have been screened for eligibility and of these, 43 (72%) were eligible at time of consent.
- 24 (53% of eligible) were consented and enrolled into the RCT study; 6 (13% of eligible) were consented and enrolled in the observational study
- We have now reached 9% of our total enrollment. No patients have completed the study.

Study design: Multi-center, prospective phase III randomized clinical trial.

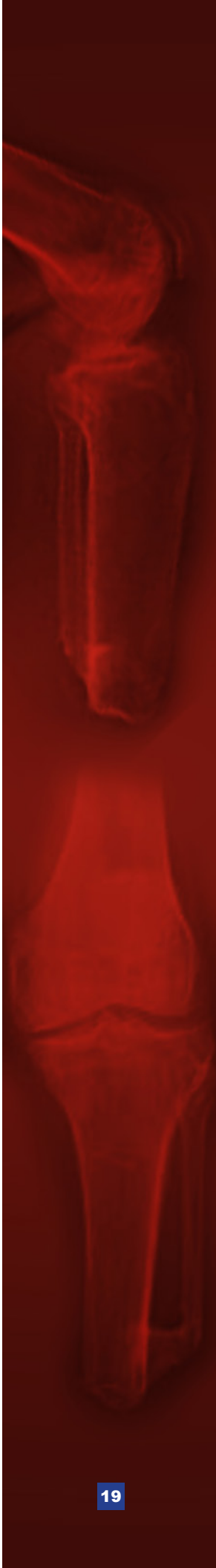
Study duration: 51 months (30 month enrollment period, 18 month patient follow up and 3 month data analysis period). Participants will be followed for 18 months after injury.

Sample size: 250 participants (125 per arm).

Number of study centers: 23 core and satellite centers.

Principal Inclusion criteria: Transtibial amputation regardless of underlying injury.

Protocol committee: M Bosse, MD, L Cannada, MD, W Ertl, MD,W Gordon, MD, C Jones, MD, G Klute, PhD, T Miclau, MD, S Morshed, MD, W Racette CPO, R Firoozabadi, MD, R Seymour, PhD, B Steverson RN, MHA, CCRP, R Teasdall, MD, CDR, J Toledano, MD, J Wenke, PhD.
From the Coordinating Center: E MacKenzie PhD, R Castillo, PhD, G deLissovoy, PhD, D Scharfstein ScD, J Luly, MS, L Reider, MHS, PhD, R Kirk, BS



Predicting Acute Compartment Syndrome using Optimized Clinical Assessment, Continuous Pressure Monitoring, and Continuous Tissue Oximetry

The PACS Study

Sponsored by: DoD CDMRP PRORP
Award Number: W8XWH-10-2-0090 (METRC II)
PI/Protocol Chair: Andrew Schmidt, MD

The primary objective of this study is to develop a tool that can aid clinicians in making a timely and accurate diagnosis of acute compartment syndrome (ACS) so that early fasciotomy can be done and unnecessary fasciotomy avoided. The secondary objective is to develop a model that accurately predicts the likelihood of ACS based on data available to the clinician within the first 48-72 hours of injury. Such data will include specific clinical findings, physiologic monitoring using muscle oxygenation measured with near-infrared spectroscopy (NIRS), continuous monitoring of intramuscular pressure (IMP) and perfusion pressure (PP), and serum markers of muscle injury (CPK levels).

There are 6 trauma centers participating in this study (6 are certified)

- 861 patients have been screened for eligibility and of these, 447 (51%) were eligible at time of consent.
- 143 (32% of eligible) were consented and enrolled into the study.
- We have now reached 71% of our total enrollment.
- 72 patients have completed the study.

Study design: Multicenter, prospective cohort study.

Study duration: 32 months (6 month planning, 6 month accrual, 6 month final follow-up, 8 month analysis and writing). Participants will be followed for six months after injury.

Sample size: 200 participants.

Number of study centers: 6 core centers.

Principal Inclusion Criteria: Closed or open (Gustilo Type I, II or IIIA) tibial shaft or tibial plateau fractures occurring in the proximal half of the tibia, or severe soft tissue injuries or crush injuries to the lower leg resulting from a high-energy mechanism or gunshot wound.

Protocol committee: A Schmidt, MD, E Carroll, MD, M Bosse, MD, J Evans, MD, R Hayda, MD, R O'Toole, MD, R. Seymour, PhD. J.R. Westberg.
From the Coordinating Center: E MacKenzie, PhD, R Castillo, PhD, D Scharfstein, ScD, V Zippunikov, PhD, S Collins, MS, G. Ha, PhD, K Frey RN, MPH.

Improving Pain Management in High Energy Orthopedic Trauma:

The PAIN Study

Sponsored by: DoD CDMRP PRORP
Award Number: W8XWH-10-2-0090 (METRC II)
Co-PI/Protocol Co-Chairs: Renan C. Castillo, PhD and Srinivasa N. Raja, MD

The primary objective of this study is to test whether adjunctive analgesic therapy during the pre and peri-operative period, in addition to standard of care pain management, can improve overall pain control and pain related outcomes without increasing analgesic related side effects. Participants will be randomized into three groups: (Group 1) standard pain management plus oral placebo for up to two weeks and intravenous and oral placebo for up to 48 hours at each surgical procedure; (Group 2) standard pain management plus oral NSAIDS (meloxicam) for up to two weeks and intravenous ketorolac and oral placebo for up to 48 hours at each surgical procedure; or (Group 3) standard pain management plus oral pregabalin for up to two weeks and intravenous placebo and oral pregabalin for up to 48 hours at each surgical procedure. The secondary objective is to estimate the incremental cost effectiveness of each adjunctive therapy relative to standard of care analgesic therapy in the treatment of severe lower limb fractures.

There are 21 trauma centers participating in this study (16 are certified)

- 163 patients have been screened for eligibility and of these, 45 (28%) were eligible at time of consent.
- 14 (31% of eligible) were consented and enrolled into the study.
- We have now reached 2% of our total enrollment
- 0 patients have completed the study.

Study design: Three-arm, double blind, randomized, placebo controlled Phase III clinical trial.

Study duration: 4 years (12 month planning, 18 month accrual, 12 month final follow-up, 3 month analysis and writing). Patients will be followed for 12 months following injury.

Sample size: 495 participants (165 per arm).

Number of study centers: 21 core and satellite centers.

Principal Inclusion Criteria: Isolated, unilateral, Grade I &II open or closed pilon (distal tibial plafond), calcaneus or tallus fractures, Lisfranc dislocations, or Grade I, II or IIIA ankle fractures with associated dislocation on presentation (OTA 44B3 or 44C) requiring operative treatment with fixation, or any combination of the above injuries surgically treated as a whole.

Protocol committee: S Raja, MD, D Anderson, PhD, K Archer, PhD, MAJ B Goff, DO, A Gottschalk, MD, PhD, T Higgins, MD, M Holden, C Jones, MD, L Marsh, MD, R O'Toole, MD, P Tornetta, MD, H Vallier, MD, S Wegener, PhD.
From the Coordinating Center: R Castillo PhD, E MacKenzie PhD, G deLissovoy, PhD, D Scharfstein ScD, A Carlini, MS, T Taylor, MPH, Y Weng, MS, K Frey RN, MPH.

Multicenter Investigation of the Mechanical Determinants of Post-Traumatic Osteoarthritis

The PTOA Study

Sponsored by: NIH National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
Award Number: 1R21AR061808-01
Co-PI/Protocol Co-Chairs: Lawrence Marsh, MD and Donald D Anderson, PHD

The primary objective of this study is to measure the incidence of PTOA and chronic pain for up to 24 months following fracture reduction surgery and quantify the extent to which fracture severity and post-reduction contact stress are related to the development of PTOA. Colleagues at University of Iowa have developed techniques to measure the fracture severity which correlate strongly with PTOA development. In this multi-center feasibility study, mechanical metrics of acute injury severity and contact stress challenge will be further validated and extended to a large and geographically diverse group of patients with tibial pilon fractures treated using a range of current techniques. Making these techniques widely available for clinical research will help lay the foundation for the development of the next generation of treatment strategies for the prevention of PTOA.

There are 21 trauma centers participating in this study (16 are certified)

- 4 patients have been screened for eligibility and of these, 4 (100%) were eligible at time of consent.
- 2 (50% of eligible) were consented and enrolled into the study.
- 0 patients have completed the study.

Study design: Multicenter, prospective cohort study.

Study duration: 345 months (9 month planning, 18 month accrual, 18 month final follow-up, 6 month analysis and writing). Participants will be followed for up to two years from the time of injury.

Sample size: 150 participants.

Number of study centers: 21 core and satellite centers.

Principal Inclusion Criteria: Isolated pilon (distal tibial platform) fractures requiring operative treatment with fixation at the discretion of the treating surgeon.

Protocol committee: S Raja, MD, D Anderson, PhD, K Archer, PhD, MAJ B Goff, DO, A Gottschalk, MD, PhD, D Hak, MD, T Higgins, MD, M Holden, C Jones, MD, L Marsh, MD, R O'Toole, MD, G Russell, MD, B Sangeorzan, MD, P Tornetta, MD, H Vallier, MD, S Wegener, PhD. From the Coordinating Center: R Castillo PhD, E MacKenzie PhD, G deLissovoy, PhD, D Scharfstein ScD, A Carlini, MS, T Taylor, MPH, Y Weng, MS, K Frey RN, MPH.

Improving Activity and Quality of Life Following Lower Extremity Trauma: The Trauma Collaborative Care Study

The TCC Study

Sponsored by: DoD CDMRP PRORP
Award Number: W8XWH-10-2-0090 (METRC II)
Co-PI/Protocol Co-Chairs: Stephen Wegener, PhD and Ellen MacKenzie, PhD

The primary objective of this study is to develop and evaluate the effectiveness of Trauma Collaborative Care (TCC) in improving a composite outcome comprised of patient reported assessment of function, depression and post-traumatic stress. The TCC intervention has three multi-modal components: 1) the Trauma Survivors Network (TSN) – an integrated approach to provide efficient access to information, peer support, and self-management training; 2) training of providers to promote patient use of TSN Program services and; 3) the use of a Recovery Coach to motivate use of services and promote communication between providers and patients. The secondary objectives are to 1) evaluate differences in pain, health related quality of life, and return to usual major activity; and 2) compare use of services in the year following injury between the two groups.

There are 12 trauma centers participating in this study (12 are certified)

- 3,620 patients have been screened for eligibility and of these, 1,164 (32%) were eligible at time of consent
- 729 (63% of eligible) were consented and enrolled into the study.
- We have now reached 81% of our total enrollment
- 32 patients have completed the study

Study design: Multicenter cluster design.

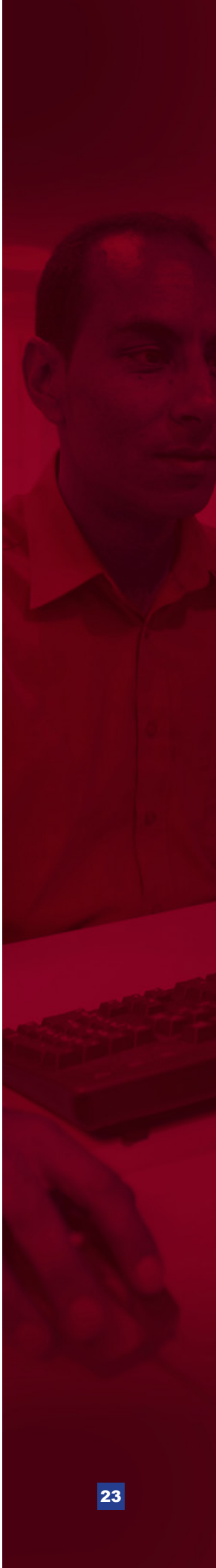
Study duration: 4 years (18 month planning, 12 months developing TCCI, 12 month accrual, 12 month final follow-up, 6 month analysis and writing). Participants will be followed for one year from the time of injury.

Sample size: 900 participants (450 per arm).

Number of study centers: 12 core and satellite centers.

Principal Inclusion Criteria: Patients treated surgically for one or more orthopaedic injuries of AIS 3 or greater with initial admission to the trauma service of the participating hospital and a length of stay >=5 days or >= 3 days with planned readmission for additional procedures, or patients with a direct admission from the initial hospitalization to an inpatient rehabilitation or subacute care facility.

Protocol committee: S Wegener, PhD, M Bosse, MD, A Bradford, PhD, R Hymes, MD, C Jones, MD, D Sietsema, PhD, RN, H Vallier, MD, R. Seymour, PhD. From the Coordinating Center: E MacKenzie, PhD, R Castillo, PhD, G deLissovoy, PhD, D Scharfstein ScD, S Collins, MS, Y Huang, MS, K Frey RN, MPH.



Streamlining Trauma Research Evaluation with Advanced Measurement:

STREAM Study

Sponsored by: NIH National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
Award Number: 1R01AR064066-01
PI/Protocol Chair: Renan Castillo, PhD

The primary objective of this study is to evaluate the reliability and responsiveness of PROMIS tools in orthopaedic trauma patients. As part of the NIH Roadmap initiative, PROMIS (Patient Reported Outcomes Measurement Information System) has developed tools, including item banks, short forms and computer-adaptive tests (CATs) that can help standardize measurement for many health-related quality of life domains. These tools are being tested in large general population samples across the lifespan. The PROMIS will assess the performance and research utility of these new tools in an orthopaedic trauma patient population for future comparative effectiveness research projects.

There are 40 trauma centers participating in this study (27 are certified)

- 95 patients have been screened for eligibility and all were eligible at time of consent.
- 80 (84% of eligible) were consented and enrolled into the study
- We have now reached 8% of our total enrollment

Study design: Multi-center, prospective longitudinal observational study.

Study duration: 3 years (6 month planning, 12 month accrual, 12 month final follow-up, 6 month analysis and writing). Patients will be followed for up to 12 months from the time of injury.

Sample size: 1000 participants.

Number of study centers: 40 core and satellite centers.

Principal Inclusion Criteria: Patients currently enrolled in the METRC FIXIT, OUTLET, TAOS and Pain studies.

Protocol committee: R O'Toole, MD, M Bosse, MD, S Wegener, PhD, S Morshed, MD, J Agel, MA, M Weaver, MD, T Higgins, MD, W. Obremskey, MD. From the Coordinating Center: R Castillo, PhD, E MacKenzie, PhD, K Chan, PhD, A Wu, PhD, D Scharfstein ScD, R Kirk, BS, A Carlini, MS, L Reider, MS, K Frey RN, MPH

Supplemental Perioperative Oxygen to Reduce Surgical Site Infection After High Energy Fracture Surgery

The Oxygen Study

Sponsored by: DoD CDMRP PRORP
Award Number: W81XWH-12-1-0588
PI/Protocol Chair: Robert V. O'Toole, MD MSME

The primary objective of this study is to assess the efficacy of supplemental perioperative oxygen in the prevention of surgical site infections for patients who experience high-energy tibial plateau, pilon, or calcaneous fractures, treated with plate and screw fixation. Secondary objectives are to 1) compare bacterial species and antimicrobial susceptibilities in the patients who develop surgical site infections in study patients treated with supplemental perioperative oxygen compared to those who were not treated with supplemental oxygen; 2) to validate the previously developed risk prediction model for the development of surgical site infections after fracture surgery; and 3) to measure and compare resource utilization and cost associated with surgical site infection in study patients treated with supplemental perioperative oxygen compared to those who were not treated with supplemental perioperative oxygen.

There are 19 trauma centers participating in this study (6 are certified)

- 268 patients have been screened for eligibility and of these, 158 (59%) were eligible at the time of consent.
- 121 (77% of eligible) were consented and enrolled into the study.
- We have now reached 81% of our total enrollment

Study design: Double Blinded Prospective Randomized Controlled Trial

Study duration: 36 months; 18 month enrollment period; 12 month patient follow-up; 6 month data analysis period

Sample size: 1000 participants (500 per arm).

Number of study centers: 19 core and satellite centers.

Principal Inclusion Criteria: High-energy tibial plateau, pilon and calcaneous fractures treated operatively with plate and screw fixation

Protocol committee: R O'Toole, MD, MSME, G Altman, MD, C Arndt, RN, M Bosse, MD, A Dagal, MD, JC D'Alleyrand, MD, T Dipasquale, DO, J Gary, MD, A Holmes, MS, M Joshi, MD, M Karunakar, MD, C Murray, MD, N Rao, MD, M Sen, MD, A Schmidt, MD, R Sikorski, MD, P Watkins, RN, M Weaver, MD
From the Coordinating Center: R Castillo, PhD, E MacKenzie, PhD, G de Lissovoy, PhD, D Scharfstein, ScD, Y Weng, MS, L Allen, MA, T Taylor, MPH

A Prospective Randomized Trial to Assess PO versus IV Antibiotics for the Treatment of Early Post-op Wound Infection

The POvIV Study

Sponsored by: DoD CDMRP PRORP
Award Number: W81XWH-10-2-0133
PI/Protocol Chair: William T. Obremskey, MD, MPH

The primary objective of this study is to investigate the efficacy of oral (per os, (PO)) antibiotic therapy versus intravenous (IV) antibiotics in the treatment of acute infection after fixation of fractures or fusion of joints. The secondary objective is to build and validate a risk prediction model for failure of treatment of early post-op wound infections after fixation of fractures.

Patients with post-operative infections routinely receive up to six weeks of intravenous antibiotic therapy following surgical debridement, despite growing evidence that oral antibiotic therapy is equally effective, with a reduced risk of complications and lower medical costs. The equivalence of oral versus intravenous therapy to treat wound infection after fixation of extremity fractures has not been definitively established in a randomized clinical trial.

There are 23 trauma centers participating in this study (12 are certified)

- 271 patients have been screened for eligibility and of these, 87 (32%) were eligible at time of consent.
- 38 (44% of eligible) were consented and enrolled into the study.
- We have now reached 14% of our total enrollment
- 1 patient has completed the study

Study design: Phase III randomized controlled clinical trial. Patients who refuse randomization or are unable to participate in the RCT due to financial issues are eligible to enroll in an observational arm.

Study duration: 4 years (6 month planning, 24 month accrual, 12 month follow-up, 6 month analysis and writing). Participants are followed for 12 months following diagnosis of infection.

Sample size: 264 participants (132 per arm).

Number of study centers: 23 core and satellite centers.

Principal Inclusion Criteria: Patients with fractures (defined as femurs, tibias, and fibulas of the legs, and the humeri, radii, and ulnas of the arms) treated with a plate or IMN, or patients undergoing fusion of subtalar, ankle, knee, wrist or elbow that develop a post op wound infection.

Protocol committee: W Obremskey, MD, MPH, J Anglen, MD, K Archer, PhD, DPT, M Bosse, MD, M Fleming, MD, M Holden, CDR J Keeling, MD, T Miclau, MD, S Morshed, MD, MPH, LTC C Murray, MD, A Schmidt, MD, T Talbot, MD, MPH, P Tornetta, III, MD, H Vallier, MD.
From the Coordinating Center: R Castillo PhD, E MacKenzie PhD, G deLissovoy, PhD, D Scharfstein ScD, A Carlini, MS, T Taylor, MPH, J DeSanto, RN, MS.

Local Antibiotic Therapy to Reduce Infection after Operative Treatment of Fractures at High Risk of Infection: A Multicenter, Randomized, Controlled Trial

The VANCO Study

Sponsored by: DoD CDMRP PRORP
Award Number: W81XWH-10-2-0134
PI/Protocol Chair: Robert V. O'Toole, MD, MSME

The VANCO Study was submitted to the JHSPH IRB on April 3, 2014. It is pending final approval.

Target date for enrollment is January, 2015.

The primary objective of this study is to assess the efficacy of local vancomycin powder in the prevention of surgical site infections for patients who experience high-energy tibial plateau and pilon fractures, treated operatively with plate and screw fixation. Secondary objectives are to 1) compare antibiotic sensitivities of the bacteria in patients who develop deep surgical site infections in study patients treated with local vancomycin powder compared to those treated without local vancomycin powder; and 2) to build and validate a risk prediction model for the development of deep surgical site infections in patients treated without local vancomycin powder and, relatedly, to explore whether the effect of the local vancomycin powder is modified by the predicted risk of infection.

Study design: Prospective Randomized Controlled Trial

Study duration: 24 months; 12 month enrollment period; 6 months of patient follow-up; 6 month data analysis period

Sample size: 1000 participants (500 per arm).

Number of study centers: 25 core and satellite centers.

Principal Inclusion Criteria: High-energy tibial plateau and pilon fractures treated operatively with plate and screw fixation

Protocol committee: R O'Toole, MD MSME, M Bosse, MD, D Chan, MD, M Graves, MD, D Hak, J Hsu, MD, MD, M Joshi, MD, H Mir, MD, C Murray, MD, N Rao, Z Roberts, MD, MD, D Sietsema, PhD RN, D Tsukayama, MD.
From the Coordinating Center: R Castillo, PhD, E MacKenzie PhD, D Scharfstein ScD, A Carlini, MS, L Allen, MA, T Taylor, MPH

Patient Response to an Integrated Orthotic and Rehabilitation Initiative for Traumatic Injuries

The PRIORITI-MTF Study

Sponsored by: DoDTATRC and CRMRP
Award Number: W81XWH-12-2-0032
Co-PI/Protocol Chair: LTC Joe Hsu, MD & Ellen MacKenzie, PhD

Two of the three MTFs have started enrolling. One MTF is pending IRB approval.

- A total of 13 patients have been screened and of these 7 (54%) have been enrolled.
- We have now reached 7% of our total enrollment goal

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). The secondary objectives of the study are to 1) document patterns of device use, use of ambulatory aids, shoe wear and patient reported satisfaction associated with the Intrepid Dynamic Exoskeletal Orthosis (IDEO); and 2) 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.

Study design: Multicenter before-after program evaluation 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.

Number of study centers: 3 MTFs.

Principal Inclusion Criteria: Patients who are currently two or more years out from a traumatic unilateral lower extremity injury at or below the knee at or below the knee, who are able to bear weight and who 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.

Protocol committee: LTC J Hsu, MD, M Bosse, MD, CDR D Dromsky, MD, J Ferguson CPO, LTC DA Gajewski MD, W Gordon, MD, R Hooper PT, PhD, J Owens MPT, LTC, BK Potter MD, COL (Ret.) C Scoville PT, Capt J Town NC. From the Coordinating Center: E MacKenzie PhD, M Bosse MD, R Castillo PhD, G deLissovoy, PhD, D Scharfstein ScD, A Carlini, MS, S Collins, MS, J DeSanto, RN, MS.

Prosthetic Fit Assessment in Transtibial Amputees Secondary to Trauma

The ProFit Study

Sponsored by: DoD PRORP
Award Number: OR130357
PI/Protocol Chair: Saam Morshed, MD, MPH, PhD

The master protocol is pending JHSPH IRB approval. The study team is working closely with sites to partner with local CPOs in preparation for training and patient assessment.

The aims of this study address an exploratory endpoint in the Major Extremity Trauma Research Consortium (METRC) Transtibial Amputation Outcomes Study (TAOS) that is investigating prosthesis fit, alignment and condition of the residual limb. As there are no validated measures of fit and alignment (factors known to impact comfort, function and performance among amputees) the TAOS study includes a provision in the protocol for acquisition of photographs, video and radiographs during the 18 month study visit in order to help develop uniform assessments of the residual limb. The goal of this study is to use these data to validate and refine the prosthetic assessment tool (ProFit) that was developed by an expert panel of certified orthotist prosthetistis (CPOs) in collaboration with orthopaedic trauma investigators, a measurement scientist and a biomedical engineer from the BADER consortium.

Study design: Multicenter, prospective study ancillary to the METRC TAOS trial.

Study duration: 36 months (7 month planning and training period, 19 month data collection period, 4 month data evaluation period conducted by CPO panel, and 6 month data analysis and writing).

Sample size: 120 TAOS patients will provide adequate power to detect important differences in fit and alignment. A subset of 60 patients is necessary to detect significant differences in alignment using the Smart Pyramid, a socket mounted device that measures forces on the prosthesis during walking. These data will be collected at 6 and 18 months following amputation and will be used in validating the ProFit assessment.

Number of study centers: 23 core and satellite centers.

Principal Inclusion Criteria: Patients requiring a unilateral transtibial amputation following major limb trauma regardless of when the injury occurred.

Protocol committee: S Morshed, MD, M Bosse, MD, M Garibaldi, CPO, K Kaufman PhD, K Chan PhD, R Seymour PhD.
From the Coordinating Center: RE MacKenzie PhD, L Reider PhD; J Luly MS; R Kirk BS

Funding Sources

The activities of METRC are currently funded exclusively by federal grants. Core funding for METRC is provided through the Orthopaedic Extremity Trauma Research Program (OETRP) (Award # W81XWH-09-2-0108) (METRC 1) and a cooperative agreement with the DoD Peer Reviewed Orthopaedic Research Program (PRORP) of the Congressionally Directed Medical Research Program (CDMRP) (Award # W81XWH-10-2-0090) (METRC 2). These awards provide funding for specific studies and support the infrastructure of the Consortium. Six of our METRC Investigators have successfully obtained individual grants that use the METRC consortium as a foundation for the research. These individuals are the prime recipients of the awards (three from DoD CDMRP, two from NIH NIAMS and one from the DoD Clinical Telemedicine & Advanced Technology Research Center (TATRC) and the Clinical and Rehabilitative Medicine Research Program (CRMRP) but they subcontract with the Coordinating Center to help with the design, implementation, and analysis of the studies. These subcontracts also provide funding to support the participation of METRC Centers in the study. A summary of these awards (total amounts) is provided on the following page.

Overview of 6-Year Budget - METRC Coodinating Center

PROJECT Studies Covered	**METRC 1** FIXIT, Bioburden, pTOG, Acetab, RetroDefect	**METRC 2** PACS, Outlet, TAOS, PAIN, TCCS	**University of Maryland PRORP #1** VANCO	**University of Maryland PRORP #2** OXYGEN	**Vanderbilt University PRORP** POvIV	**University of Iowa NIH R21** PTOA	**Johns Hopkins TATRC** PRIORITI	**Univ of California San Fran** PROFIT	**Johns Hopkins NIH R01** STREAM	**TOTAL**
MCC Operational BUDGET										
Personnel	3,135,912	5,834,433	839,948	206,994	332,973	46,341	274,864	116,039	469,574	**11,257,078**
Other Direct Costs	674,127	1,874,374	173,720	55,144	30,431	2,748	103,679		145,280	**3,059,503**
Equipment and Major Supplies		1,540,220	3,375		76,770				23,896	**1,640,886**
Civilian Centers BUDGET										
Core Civilian	9,831,462	14,777,933								**24,609,395**
Patient Enrollment	2,490,000	3,983,500	2,300,000*	1,112,000*	600,000*	75,000*	27,000*		250,000*	**10,837,500**
MTF Centers BUDGET										
Direct Costs	2,689,694	1,989,540					1,827,520			**6,506,754**
SUMMARY MCC BUDGET										
MCC Direct Costs	18,821,195	30,000,000	3,313,668	1,374,138	1,040,174	124,089	2,233,063	116,039	888,750	**57,911,116**
MCC Indirect Costs	2,678,430	8,657,995	361,350	387,577	141,735	76,935	266,937	71,944	551,025	**13,193,928**
Total Award	21,499,625	38,657,995	3,675,018	1,761,715	1,181,909	201,024	2,500,000	187,983	1,439,775	**71,105,044**

* *These amounts may be used to support patient enrollment in either cores, military training facilities or satellite centers*

Looking Forward

As we look forward to the coming year we must continue to focus on study enrollment and continuous quality improvement activities. At the same time we will be entering the exciting phase of data analysis and begin to provide evidence to guide the care of the extremity trauma patient at podium venues in 2015. We recognize the efforts of all our core and satellite centers and thank them for their unwavering commitment to the goals of the consortium.

We continue to cultivate new research ideas that address the priorities of the Department of Defense and METRC. Currently under discussion are studies to:

- ✔ Investigate the advantages of early versus delayed weight bearing for selected closed fractures of the femur, tibia and ankle (PI: William M. Ricci, MD);
- ✔ Compare the relative effectiveness of the Intrepid Dynamic Exoskeletal Orthosis (IDEO) with a custom Patellar Tendon Bearing (PTB) ankle foot orthosis in civilian adults with chronic muscle weakness and functional deficits present at 2 or more years following a traumatic injury below the knee (PI: Joseph R. Hsu, MD);
- ✔ Test the efficacy of physical therapy (PT) enhanced by partial arterial inflow restriction when compared to usual care PT alone (PI: Johnny G. Owens, MPT);
- ✔ Examine the effectiveness of early surgical treatment of severe multiligamentous knee injuries (PI: William T. Obremskey, MD, MPH);
- ✔ Investigate the effect of using patient incentive payments to reduce complications associated with smoking and tobacco use following lower extremity trauma (PI: Renan C. Castillo, PhD);
- ✔ Evaluate long term health outcomes following major limb trauma sustained in OIF/OEF/OND and compare these outcomes following amputation vs. limb salvage. Use of services and outcomes will be compared for those injured early (2003-2007) and later (2008- 2013) in OIF/OEF/OND (PI: Ellen J. MacKenzie PhD);
- ✔ Conduct a Multi-Center Prospective Observational Study of Nerve Repair and Reconstruction Associated with Major Extremity Trauma (PI: Jaimie T. Shores, MD).

Please continue to check our website **www.metrc.org** to monitor the progress of our activities.

Appendix A

Participating Centers

MILITARY TREATMENT FACILITIES

San Antonio Military Medical Center, BAM
Principal Investigator: MAJ Daniel Stinner, MD

Walter Reed National Military Medical Center, WRD
Principal Investigator: LTC Wade T. Gordon, MD

Naval Medical Center Portsmouth, NPM
Principal Investigator: LCDR Christopher Smith, MD

Naval Medical Center San Diego, NSD
Principal Investigator: CDR James E. Toledano, MD, MC, USN

CORE CIVILIAN SITES

Boston Medical Center, BMC
Principal Investigator: Paul Tornetta, III, MD

Carolinas Medical Center, CMC
Principal Investigator & Chair of the METRC Consortium: Michael J. Bosse, MD

Denver Health and Hospital Authority, DHA
Principal Investigator: David J. Hak, MD, MBA

Florida Orthopaedic Institute / Tampa General & St. Joseph's Hospitals, FOI
Principal Investigator: Roy W. Sanders, MD

Hennepin County Medical Center / Regions Hospital, MIN
Principal Investigators: Andrew H. Schmidt, MD & Paul Lafferty, MD

MetroHealth Medical Center, MET
Principal Investigator: Heather A. Vallier, MD

Methodist Hospital, MTH
Principal Investigator: Todd McKinley, MD

Orthopaedic Associates of Michigan / Spectrum Health, SPC
Principal Investigator: Clifford B. Jones, MD

Penn State University M.S. Hershey Medical Center, PSU
Principal Investigator: J. Spence Reid, MD

St. Louis University Hospital, STL
Principal Investigator: Lisa K. Cannada, MD

University of California at San Francisco, USF
Principal Investigator: Theodore Miclau, III, MD

University of Iowa Hospitals & Clinics, UIA
Principal Investigator: J. Lawrence Marsh, MD

University of Maryland R Adams Cowley Shock Trauma Center, UMD
Principal Investigator & Co-Chair of the METRC Consortium: Andrew N. Pollak, MD

University of Miami Ryder Trauma Center, RYD
Principal Investigator: Gregory A. Zych, DO

University of Mississippi Medical Center, UMS
Principal Investigator: George Russell, MD

University of Oklahoma Medical Center, UOK
Principal Investigator: David Teague, MD

University of Pittsburgh, PIT
Principal Investigator: Andrew R. Evans, MD

University of Texas Southwestern Medical Center, UTX
Principal Investigator: Adam J. Starr, MD

University of Washington / Harborview Medical Center, UWA
Principal Investigator: Reza Firoozabadi, MD

UT Health: The University of Texas Health Science Center at Houston, HOU
Principal Investigator: Joshua Gary, MD

Vanderbilt University Medical Center, VMC
Principal Investigator: William T. Obremskey, MD, MPH

Wake Forest University Baptist Medical Center, WFU
Principal Investigator: Eben Carroll, MD

SATELLITE CENTERS

Allegheny General Hospital, AGY
Principal Investigator: Gregory Altman, MD

Barnes-Jewish Hospital at Washington University, BJH
Principal Investigator: William M. Ricci, MD

Ben Taub General Hospital, BEN
Principal Investigator: Jack Dawson, MD

Duke University Hospital, DUK
Principal Investigator: Robert D. Zura, MD

Eastern Maine Medical Center, EME
Principal Investigator: David Carmack, MD

Eskenazi Health, ESK
Principal Investigator: Jeffrey Anglen, MD

Emory University, EMU
Principal Investigator: William M. Reisman, MD

Foothills Medical Center, CGY
Principal Investigator: Richard Buckley, MD

Geisinger Health System, GMC
Principal Investigator: Michael Suk, MD, JD, MPH, FACS

Grant Medical Center, GRT
Principal Investigator: Benjamin Taylor, MD

Harvard Orthopaedic Trauma Service, HRV
Principal Investigator: Michael Weaver, MD

Inova Fairfax Hospital, IFH
Principal Investigator: Robert A. Hymes, MD

Jamaica Hospital Medical Center, JAM
Principal Investigator: Sanjit Konda, MD

Johns Hopkins University, JHU
Principal Investigator: Greg Osgood, MD

Louisiana State University Health Sciences Center, SHV
Principal Investigator: Massimo Morandi MD, FACS

Louisiana State University, LSU
Principal Investigator: Peter C. Krause, MD

Mission Hospital, ASH
Principal Investigator: Harold M. Frisch, MD

Mountain States Health Alliance, JCM
Principal Investigator: Robert Harris, MD

NYU Langone Medical Center, LMC
Principal Investigator: Sanjit Konda, MD

Ohio State University Medical Center, OSU
Principal Investigator: Laura Phieffer, MD

Regional Medical Center at Memphis, CAM
Principal Investigator: John Weinlein, MD

Rhode Island Hospital, Brown University, RIH
Principal Investigator: Roman A. Hayda, MD

Scott and White Memorial Center, SWM
Principal Investigator: Michael Brennan, MD

Stanford University Medical Center, STN
Principal Investigator: Julius A. Bishop MD

St. Mary's Medical Center, STM
Principal Investigator: Thomas Saylor, MD

St Luke's University Health Network, LUK
Principal Investigator; Stanislaw Stawicki, MD

St Vincent Indianapolis Hospital, STV
Principal Investigator; Renn Crichlow, MD

Temple University Hospital, TMP
Principal Investigator: Saqib Rehman, MD

University of Alabama at Birmingham, UAB
Principal Investigator: Jason Lowe, MD

University of Kansas Medical Center, UKS
Principal Investigator: Michael Tilley, MD

University of Pennsylvania, PEN
Principal Investigator: Samir Mehta, MD

University of Rochester, ROC
Principal Investigator: John T. Gorczyca, MD

University of Utah, UUT
Principal Investigator: Thomas F. Higgins, MD

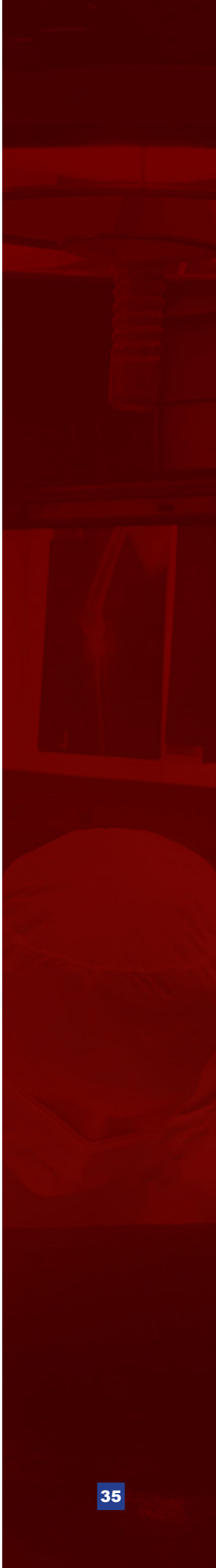
University of Virginia Medical Center, UVA
Principal Investigator: David B. Weiss, MD

University of Wisconsin, UWI
Principal Investigator: Christopher Doro, MD

William Beaumont Hospital, OAK
Principal Investigator: Kevin Grant, MD

Wright State University, WSU
Principal Investigator: Michael Prayson, MD

York Hospital / WellSpan Health, YRK
Principal Investigator: Thomas DiPasquale, DO, FACOS, FAOAO



Appendix B

Staff of the Coordinating Center

Ellen J. MacKenzie, PhD, Director

Renan C. Castillo, PhD, Deputy Director

Daniel O. Scharfstein, ScD, Principal Biostatistician

Gregory deLissovoy, PhD, MPH, Principal Economist

Lisa Reider, PhD, Associate Director

Katherine Frey, RN, MPH, MS, Associate Director

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Lauren Allen, MA, Director, Monitoring, Training and Quality Improvement

Lance Brown, MBA, Financial Manager

Anthony R. Carlini, MS, Director, Informatics

Susan Collins, MSc, Study Manager

Jennifer Desanto, MS, RN, Study Director

Cathy Epstein, BA, Administrative Coordinator

Grace Ha, PhD, Director, CRF Development and Maintenance

Andre Hackman, MS, Senior Programmer

Rachel Holthaus, MS, CIP, Director, Finance, Administration and Regulatory Oversight

Yanjie Huang, ScM, BM, Data Analyst

Rachel Kirk, BS, Study Manager

Jason Luly, MS, Biostatistician

Greg Mettee, BS, Research Assistant

Christina Owens, BS, Research Assistant

Steve Samudrala, MS, Programmer Analyst

Na Tan, MBA, Budget Analyst

Tara Taylor, MPH, Study Manager

Yingjie Weng, MHS, Data Analyst

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