

2011

ANNUAL REPORT



METRC

Major Extremity Trauma Research Consortium

Report Documentation Page

Form Approved
OMB No. 0704-0188

Public reporting burden for the collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to a penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number.

1. REPORT DATE 2011		2. REPORT TYPE		3. DATES COVERED 00-00-2011 to 00-00-2011	
4. TITLE AND SUBTITLE Major Extremity Trauma Research Consortium (METRC) 2011 Annual Report				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S)				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Major Extremity Trauma Research Consortium, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, 21205				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION/AVAILABILITY STATEMENT Approved for public release; distribution unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT					
15. SUBJECT TERMS					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT unclassified	b. ABSTRACT unclassified	c. THIS PAGE unclassified			



Contents

- 1 Letter from the Chair and the Director of the Coordinating Center**
- 2 About METRC**
- 6 Developing the Infrastructure**
- 10 The METRC Registry**
- 12 Ongoing Research**
- 28 Sources of Funding**
- 30 Looking Forward**

Appendices:

Table A – Participating Centers

Table B – Staff of the METRC Coordinating Center

Table C – Study Participation



Dear Colleagues and Friends,

We are pleased to present the 2010 – 2011 annual report of the Major Extremity Trauma Research Consortium (METRC).

This prestigious award from the U.S. Department of Defense and its Peer Reviewed Orthopaedic Research Program (DOD PRORP) designates our program as the leader in developing cutting edge orthopaedic treatment guidelines for the optimal care of the wounded warrior. METRC seeks to improve the clinical, functional and quality of life outcomes of both service members and civilians who sustain high energy trauma to the extremities.

We are excited by the progress the Consortium has made to date. We currently have three studies actively enrolling patients and four additional studies poised to commence by the end of 2011. While we recognize that there is significant work before us, we remain optimistic about the potential for the Consortium to fundamentally change the way extremity trauma is treated in the future.

The METRC surgeons and our Coordinating Center staff continue to effectively collaborate on the roll-out of our core projects and in extending the METRC platform to METRC investigator-initiated projects. The University of Iowa received an R-21 NIH award and the University of Maryland and Vanderbilt University received DOD PRORP individual clinical trial awards for METRC sponsored projects.

We are proud of the work the Consortium has accomplished to date and look forward to the productive partnerships that will result from our initiatives.

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 multicenter 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 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 high volumes of patients with severe injuries that are treated at major Level I trauma centers and the military treatment centers (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 24 core Level I civilian trauma centers and 4 core Military Treatment Facilities (MTFs) – with the ability to expand patient recruitment more than 26 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 multicenter 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.**

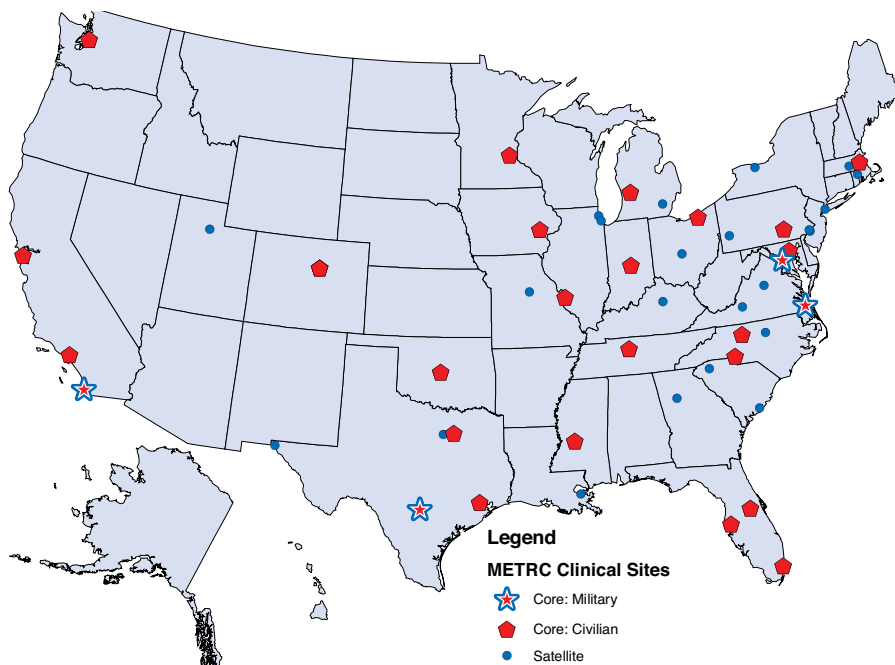
METRC is committed to conducting high quality clinical research that will make a difference in the lives of those who sustain major orthopaedic trauma. It will do so by establishing a clinical research network that is dynamic and responsive to new clinical challenges or the emergence of new, promising novel therapies. The success of the Consortium will depend 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 will also depend 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 24 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 infrastructure. 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 multicenter studies, and academic qualifications.

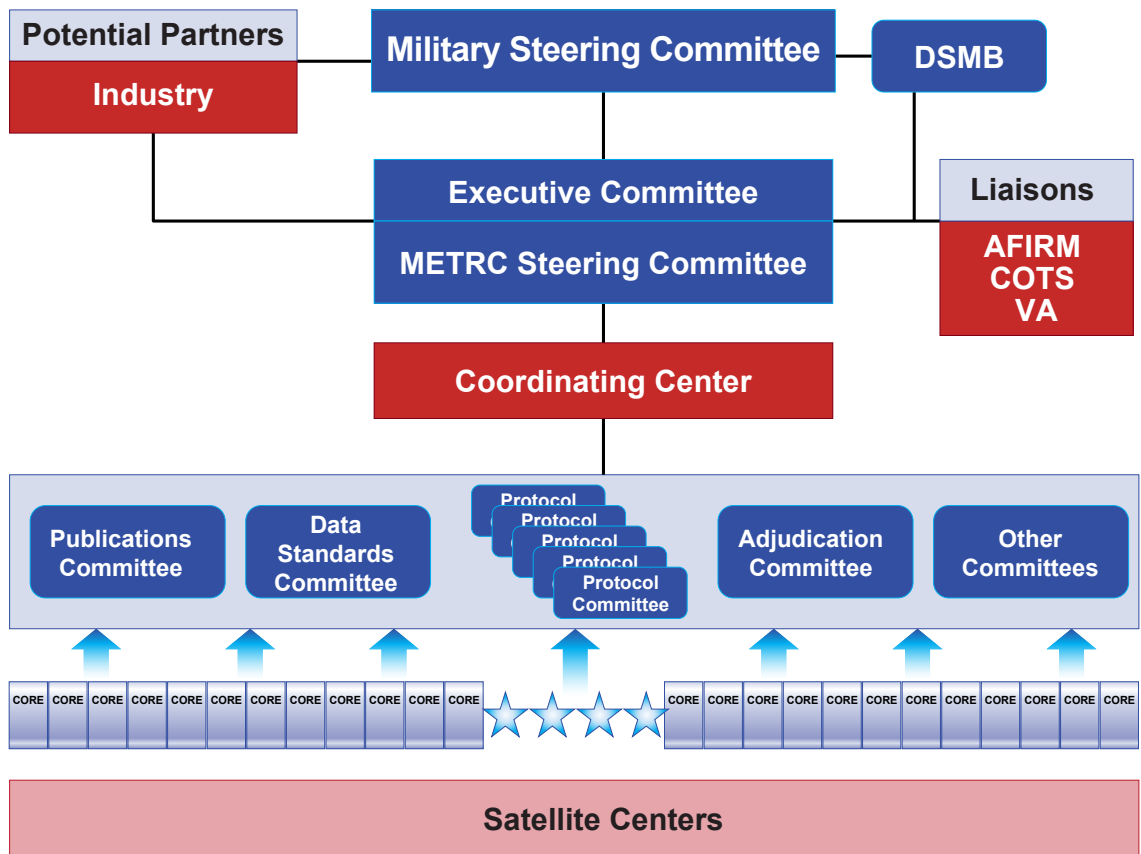
The Satellite Clinical Centers are civilian trauma centers with an orthopaedic trauma program treating at least a modest number of severe extremity injuries. They are invited to participate in individual METRC studies to ensure adequate numbers and appropriate mix of patients. Their participation is supported by a fee provided for each patient screened, enrolled and successfully followed. As of October, 2011 26 satellite centers had confirmed their commitment to METRC.



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



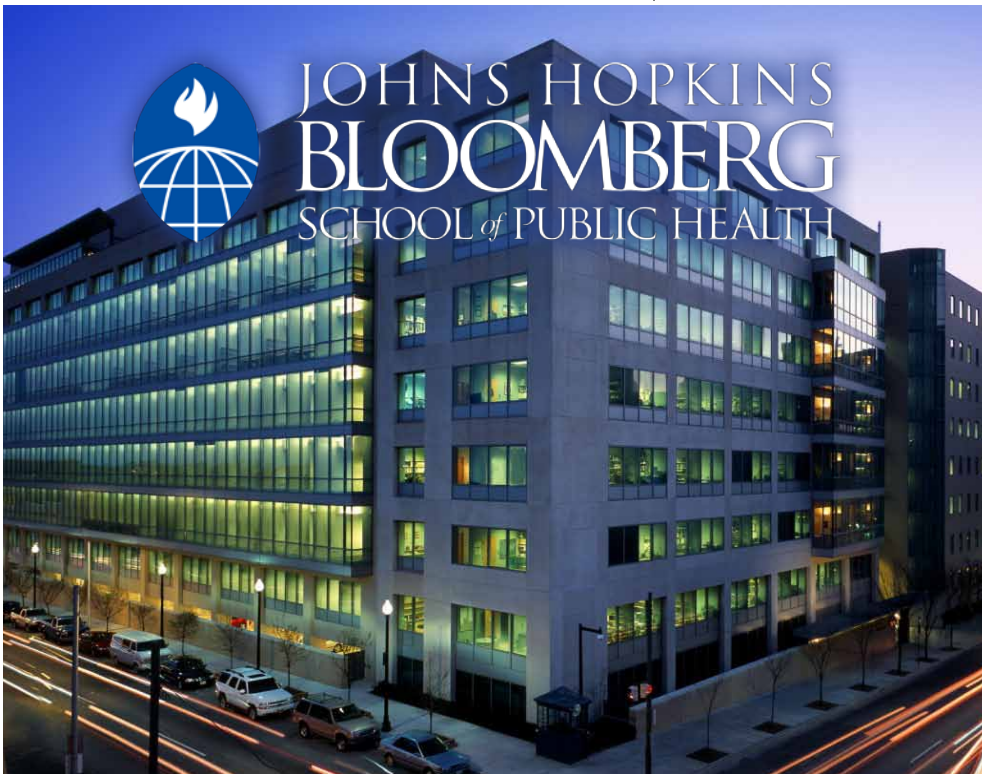
The primary decision-making body of the Major Extremity Trauma Research Consortium (METRC) is the METRC Steering Committee, which is a representative body of the investigators and the U.S. Military. It provides ongoing oversight in planning and conducting each study sponsored by the Consortium and approves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



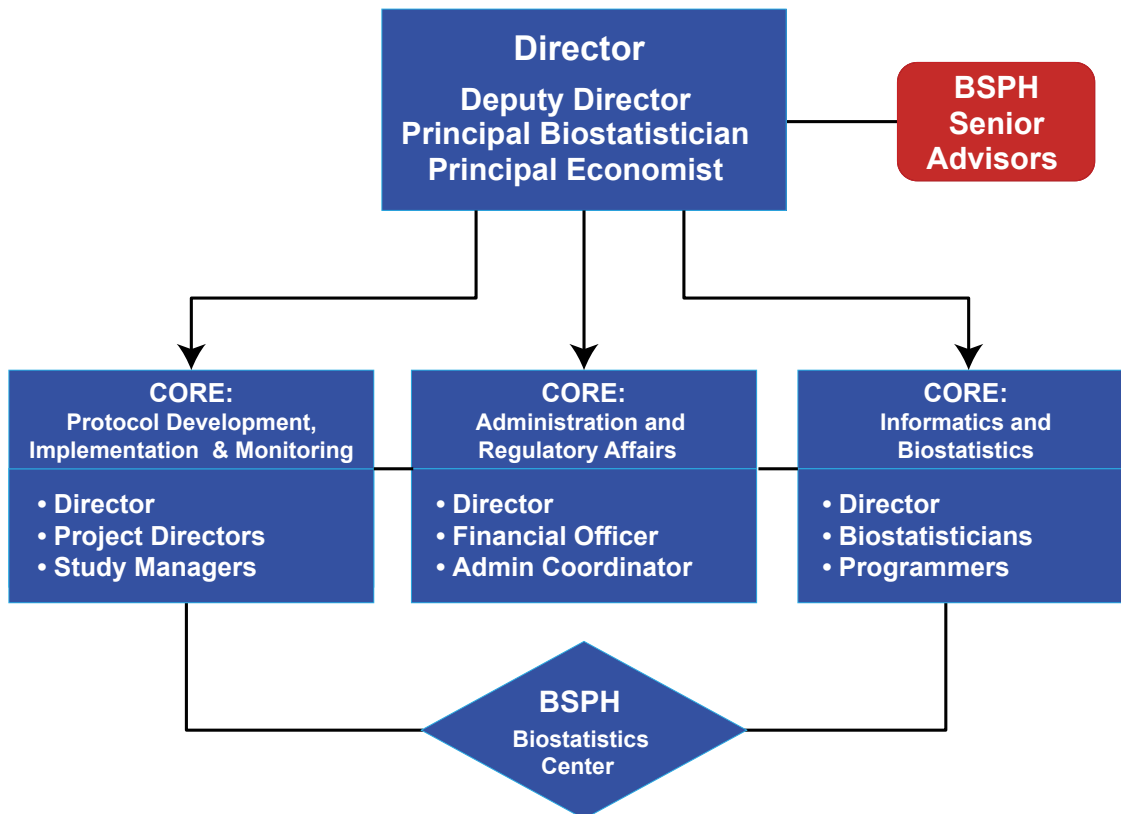
An Executive Committee serves as the agent of the Steering Committee in carrying out the day-to-day administrative responsibilities of the Consortium and Consortium-sponsored studies. The Executive Committee reviews and prepares issues for consideration by the Steering Committee. The Consortium is supported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

A Military Steering Committee has been 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 three cores: (1) Protocol Development, Implementation and Monitoring; (2) Administration and Regulatory Affairs and (3) Informatics and Biostatistics. Resources of the Johns Hopkins Bloomberg School of Public Health Biostatistics Center are used to further support the data management and analysis activities of the Center. The Director, Deputy Director, Principal Biostatistician, and Principal Economist oversee the three core activities of the Coordinating Center.



A list of key personnel of the Coordinating Center is available in the appendix as Table B.



Developing the Infrastructure

Since its establishment in 2009, METRC has developed an infrastructure to support its mission and secured funding for the initiation of 11 multicenter studies. We are currently enrolling patients in three of these studies. Another four studies are undergoing regulatory review. Protocols are currently under development for the remaining four studies. A description of the individual studies and their status as of October 1, 2011 is presented later in this report.

Here we describe the major accomplishments of the Coordinating Center in establishing the resources to facilitate the development and implementation of these studies.

Staffing the Coordinating Center: The Coordinating Center has hired several new staff members to meet the administrative and study specific demands of the Consortium; we will be hiring one additional Project Director and a masters-trained biostatistician over the coming year (see Table B in the Appendix). Once these individuals are in place we will be fully staffed for currently funded projects. Roles for the three cores and individuals within these cores have been delineated. We have re-organized the Protocol Development, Implementation and Monitoring Core so that each study sponsored by METRC will be facilitated by a team of three individuals to consist of a Lead Coordinating Center Investigator, a Project Director, and a Study Manager.

Establishing Policies and Standard Operating Procedures (SOPs):

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

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

This past year, 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 (see box) are distributed to all Site Research Coordinators and made available on the website. Amendments to these SOPs will be made as necessary.

METRC has developed Standard Operating Procedures (SOPs)

1. **METRC Overview and Policies**
2. **Coordinating Center Organization**
3. **Data Safety Monitoring Board**
4. **Study Initiation**
5. **IRB Submission and Study Documentation**
6. **Adverse Event Reporting**
7. **Data Collection and Data Management in REDCap**
8. **Clinical Site Certification**
9. **Patient Follow-up**
10. **Case Report Forms Management**
11. **Collection of Data - Medical Care Costs**
12. **Clinical Site Monitoring**
13. **Data Quality Assurance**

Facilitating Communication: Several tools have been developed by the Coordinating Center to facilitate communications among members of the METRC Consortium. First and foremost, a website has been developed that includes sections that are password protected and accessible only by certified members of the METRC Consortium (www.metrc.org). This private part of the website is used to store and distribute all official Consortium documents and resources including: descriptions and organizational charts for METRC, consortium polices and SOPs, directories for all participating sites, investigators, and consultants, meeting agendas and minutes, METRC presentations, and other documents to support the work of the consortium.

This year, two new features were added to the website. First, all materials related to a specific study can be directly accessed through the website. Posted for any given study are the protocol and master consent forms, recruitment materials, training presentations and videos, and Case Report Forms (CRFs).

In addition, a bulletin board feature was added to the website to facilitate communication among Consortium members. The bulletin board is organized into several different sections that are either general to METRC or study specific.

Web and video conferencing are a key component of the overall METRC communication strategy. Whenever possible, METRC meetings are conducted via web conferencing, which allows the sharing of documents, slide presentations, agendas, voting, private chat, audio and video. Monthly meetings of both the Steering Committee and the Site Research Coordinators are held via WebEx.



Establishing a Distributed Data

System: 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 web-based, data entry system using most web browsers to access an internet-connected database server. 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 existing features of the REDCap application: registration of all candidates for the trial; 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 (i.e., checking the correct format and range of each entered item; intra-form validation, checking for logic errors, skip pattern violations across items on a form, and inter-form validation, checking for inconsistencies across forms). METRC continues to add functionalities to the REDCap platform. These extensions are developed in a modular fashion and do not impede ongoing upgrades and patches released by the REDCap support team at Vanderbilt University.

Standardizing Data Collection and CRF Development:

Over the past year, METRC developed a Data Standards and Data Collection Policy. Core data elements were identified and will be collected uniformly across all studies except in specific studies of limited scope. Collecting core data across studies will allow us to combine and analyze outcomes across studies, compare study populations, conduct METRC-wide secondary data analyses, and serve as a starting point for Case Report Forms (CRF) development for any given study. The eleven core domains for data collection are summarized here.

In addition to developing the core data elements to be collected across all studies, we are developing standard procedures for collecting data common to many (although not all) studies. An SOP for the completion and management of METRC Case Report Forms (CRFs) has also been developed and is greatly facilitating the development of CRFs across studies.

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**

Developing Patient Recruitment Materials: The Coordinating Center developed a standard METRC brochure describing the Consortium for the purpose of motivating patients and their families to participate in studies for which they are eligible. The brochure has a pocket designed to insert a flier about each specific study. English and Spanish versions of the brochures and the inserts exist. In addition, a template for a flipchart to help in the consenting process was developed for studies in which recruitment will be particularly challenging. Finally, we developed a video for recruitment into the FIXIT study. This video will serve as a template for other studies.



Establishing the METRC Data Safety Monitoring Board (DSMB): A DSMB has been established for METRC and will act 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 will serve as Medical Monitor. Other members of the board are listed here. A charter was developed and will guide the activities of the DSMB. The full board met for the first time in June, 2011 to establish standard operating procedures and review the FIXIT and pTOG studies.

METRC Data Safety Monitoring Board

Marc Swiontkowski, MD (CHAIR)

Department of Orthopaedics
University of Minnesota

Baruch A. Brody, Ph.D.

Center for Medical Ethics and Health Policy
Baylor College of Medicine

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
Northrop Grumman

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

The METRC Registry

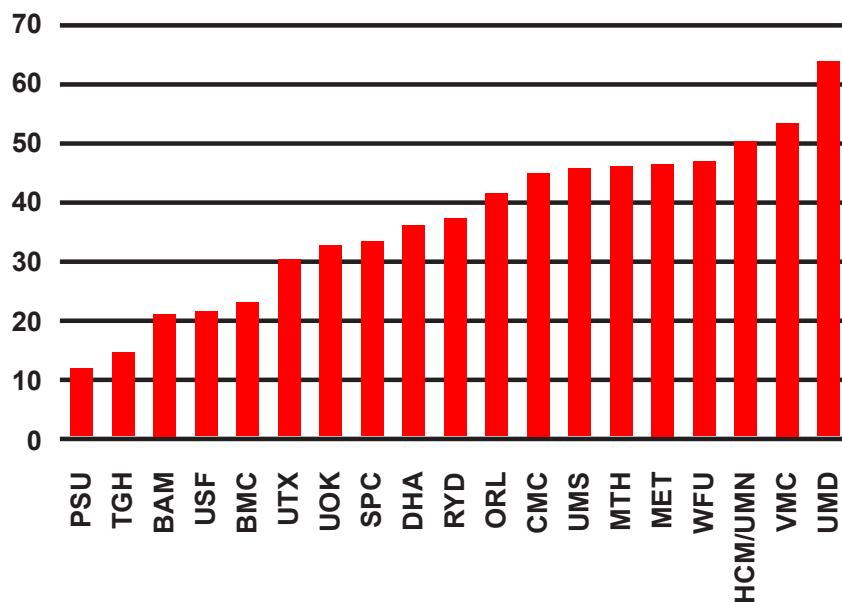
In 2010, a registry was established to assist the Consortium in determining the feasibility of future studies with adequate power to address critical research questions. All core centers were asked to implement the registry and maintain the registry for at least 365 consecutive days. The registry contains 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.

As of September 29, 2011, 19 of the 28 core centers had implemented the registry (another 4 are approved for implementation); the mean number of days centers have been entering data is 241 (range: 50-365). Two centers have received approval to implement the registry; five are pending DOD or CRADA approval; two centers are pending local IRB approval. (See Table C in the Appendix).

A total of 5,768 patients have been entered as of 12:50 (EDT) September 29, 2011. Of these, 5,723 are complete (i.e. all applicable forms have been filled out and saved by the site as complete). These patients sustained a total of 7,110 fractures (mean of 1.24 fractures per patient).

As shown in the figure, the average number of cases entered per month (corrected for total number of days since data entry began) varies by site. Given temporal trends in the incidence of major trauma, estimates for sites contributing data for only a short time may influence the estimated number of cases.

Average Registry Cases Entered per Month by Site



The table below provides the number of fractures entered in the registry by upper and lower limb and closed versus open fractures (together with limited characteristics of open fractures). A total of 130 amputations (traumatic and surgical) have been registered across the 19 sites (17 to the upper limb and 113 to the lower limbs). The mix of patients varies by site.

Number of Fractures in the Registry

(as of September 29, 2011)

Total Number of Fractures	7,110
----------------------------------	--------------

Number of Upper Limb Fractures *	1,470
Number Traumatic Amputations	8
Number Closed Fractures	1,056
Number Open Fractures	406
% Gustilo Type III	31.0%
% with bone loss	50.7%
% with loss to muscle	40.9%
% with some contamination	38.2%
% with extensive degloving	6.9%
% with arterial injury	6.4%

Number of Lower Limb Fractures *	5,628
Number Traumatic Amputations	55
Number Closed Fractures	4,334
Number Open Fractures	1,239
% Gustilo Type III	49.7%
% with bone loss	49.6%
% with loss to muscle	42.5%
% with some contamination	42.0%
% with extensive degloving	6.3%
% with arterial injury	9.8%

**Note: 12 cases with unknown data are excluded*

The Registry is currently being used to determine the incidence of specific types and severities of injuries to better inform the feasibility and design of current and future studies. In addition, two analyses of the registry data are underway:

- Registry data are being used to derive national estimates of the incidence of major limb trauma and serve as the context in which to describe the overall objectives and organization of the METRC consortium;
- Registry data are being used to examine the distribution of fractures by the Gustilo typology and elements of the new OTA classification.

Both analyses will result in manuscripts to be submitted for publication and presentation.

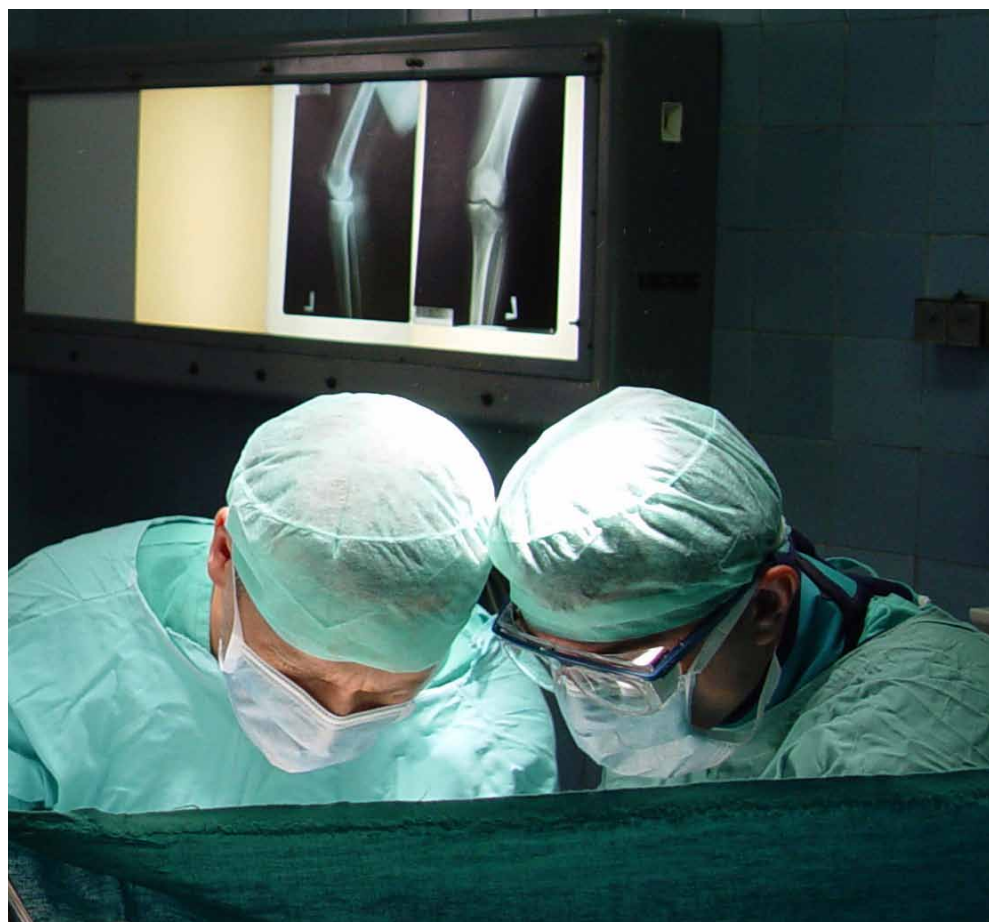
Ongoing Research of the Consortium

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 is currently funded to conduct 11 studies that address six of the seven core areas of research. At the present time there are no studies funded to address issues of wound care and closure.

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**
- **Post-Acute Care and Rehabilitation Outcomes**



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

A list of participating centers in each of the study is attached at the end of this report

(Table C in the Appendix)

DOD OETRP (core funding for METRC 1)

- **pTOG:** rhBMP-2 vs. Autograft for Critical Size Tibial Defects: A multicenter, randomized trial
STATUS: Master protocol approved; 3 sites enrolling
- **FIXIT:** A randomized controlled trial of ring external fixation vs. locked IM nail as the definitive stabilization of Grade IIIB tibia fractures
STATUS: Master protocol approved; 4 sites enrolling
- **BIOBURDEN:** Assessment of severe extremity wound bioburden at the time of definitive wound closure or coverage: correlation with subsequent post-closure deep wound infection
STATUS: Master protocol approved; 1 site enrolling

DOD CDMRP (core funding for METRC 2)

- **PACS:** Predicting acute compartment syndrome using optimized clinical assessment, continuous pressure monitoring, and continuous tissue oximetry
STATUS: Master protocol undergoing review by the Johns Hopkins IRB
- **OUTLET:** Outcomes following severe distal tibia, ankle and/or foot trauma: comparison of limb salvage vs. transtibial amputation
STATUS: Master protocol undergoing review by the Johns Hopkins IRB
- **ERTL:** Comparison of transtibial amputation with and without a tibia-fibula synostosis
STATUS: Master protocol under development
- **PAIN:** Comparing the efficacy of standard pain management vs. standard pain management combined with use of perioperative pregabalin or ketorolac in the treatment of severe lower limb fractures
STATUS: Master protocol under development
- **TCCI:** Using a collaborative care model to improve activity and quality of life following major extremity trauma
STATUS: Master protocol under development

DOD CDMRP Individual Clinical Trial Awards

- **POvIV:** A prospective randomized trial to assess PO vs. IV antibiotics for the treatment of early post-op wound infection after plate fixation of extremity fractures (primary award to Vanderbilt University)
STATUS: Master protocol undergoing review by the DOD
- **APS:** Novel therapy to reduce infection after operative treatment of fractures at high risk of infection: a multicenter randomized controlled trial (primary award to University of Maryland)
STATUS: Animal studies are ongoing in support of an IND application to FDA

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

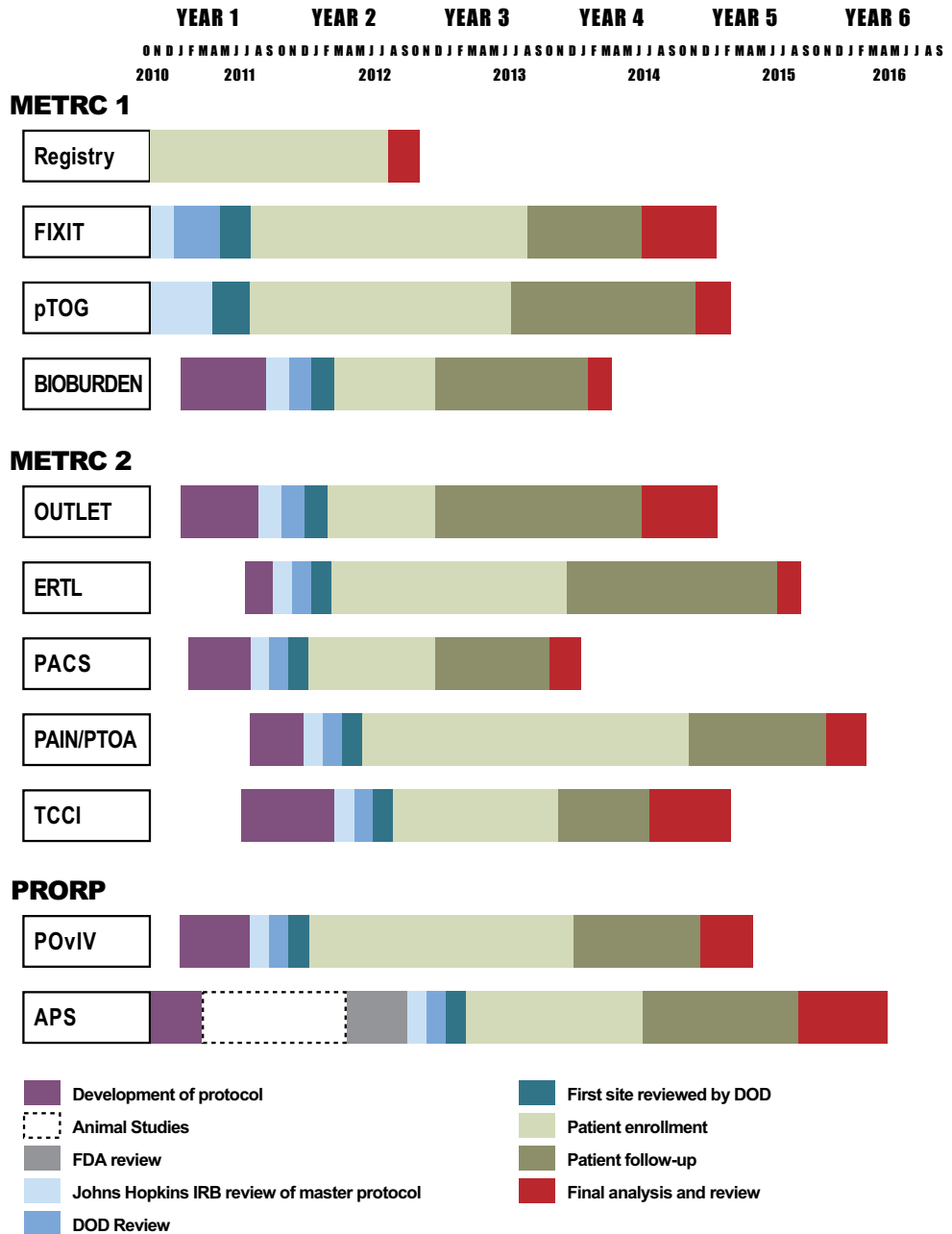
- **PTOA:** Multicenter investigation of the mechanical determinants of post-traumatic osteoarthritis (primary award to University of Iowa)
STATUS: Master protocol under development

St. Elizabeth's
Medical Center
Center for
Biomedical
Research

A timeline for the rollout of these studies has been developed and mechanisms put in place to better assure that milestones are met in a timely manner. A master METRC protocol has been developed that describes the overall organization of METRC and its standard operating procedures (SOPs) that are relevant to all studies sponsored by METRC. This master protocol has been submitted to the Johns Hopkins IRB and once approved by this IRB, it will be distributed to all core METRC centers to assist them in working with their local IRBs.

Six Year Timeline for METRC Studies

June 2011



Also, to assure that studies do not compete with each other for patients, a Study Eligibility Grid has been developed and will be maintained by the Coordinating Center (see below). All requests for studies to be sponsored by METRC are required to insert the study's proposed inclusion criteria within the grid and discuss the potential for competition of patients with other, ongoing studies.

METRC Study Inclusion Grid - Gustilo vs OTA Bone Segment

	OTA	Gustilo				
		Closed	I/II	IIIA	IIIB	IIIC
Humerus	11A,B,C	5	5	5	5	5
	12A,B,C	5	5	5	5	5
	13A,B,C	5	5	5	5	5
Radius / Ulna	21A,B,C	5	5	5	5	5
	22A,B,C	5	5	5	5	5
	23A,B,C	5	5	5	5	5
Femur	31A,B,C	5	5	5	5	5
	32A,B,C	5	5	5	5	5
	33A,B,C	5	5	5	5	5
Tibia/Fibula	41A	5 7	5 7	1 3 5 7 A	1 3 5 A	5 5
	41B	5 6 7 B	5 6 7 B	1 3 5 6 7 A B	1 3 5 6 A B	5 5 6 B
	41C	5 6 7 B	5 6 7 B	5 6 7 A B	5 6 A B	5 5 6 B
	42A	5 7	2 5 7	1 2 3 5 7 A	1 2 3 5 A	2 3 5
	42B	5 7	2 5 7	1 2 3 5 7 A	1 2 3 5 A	2 3 5
	42C	5 7	2 5 7	1 2 3 5 7 A	1 2 3 5 A	2 3 5
	43A	5 9	5 9	1 3 5 9 A	1 3 5 9 A	5 5 9
	43B	5 6 8 9 B D	5 6 8 9 B D	1 3 4 5 9 A C D	1 3 4 5 9 A C D	5 4 5 9 C D
	43C	5 6 8 9 B D	5 6 8 9 B D	5 4 5 9 A C D	5 4 5 9 A C D	5 4 5 9 C D
	44A	5 9	5 9	5 9	5 9	5 9
	44B	5 9	5 9	5 9	4 5 9 C	4 5 9 C
	44C	5 9	5 9	5 9	4 5 9 C	4 5 9 C
	Foot	81A	9	9	9	9
81B		9	9	4 9 C	4 9 C	4 9 C
81C		9	9	9	9	9
82A		6 8 9 D	6 8 D	9	9	9
82B		6 8 9 D	6 8 D	4 9 C	4 9 C	4 9 C
82C		6 8 9 D	6 8 D	4 9 C	4 9 C	4 9 C
89A,B,C		4 9 C	4 9 C	4 9 C	4 9 C	4 9 C

Traumatic Transtibial Amputation: 8

*Note: All studies have significant other inclusion/exclusion criteria to consider. Grid primarily considers Gustilo and OTA combinations.

Study	Key	Comments		
FIXIT	1	Using modified IIIA; Only certain subtypes of 41B, 43B	Pain/PTOA	9
pTOG	2		ERTL	9
Bioburden	5	Includes transtibial amps	TCCI	9
OUTLET	4	Blast foot and industrial crush foot included as 89X; only certain subtypes of 43B, 81B	Chitosan	9
				Criteria TBD
POvIV	5	Primarily infection inclusion	Oxygen	9
APS	6	High energy mechanism and timing of fixation an issue	PRIORITI	9
				Same criteria as APS(6)
PACS	7	Severe crush/severe soft tissue injury (with or without fracture) not included in grid above.	PTOA RCT	9
				To be part of OUTLET(4)
				Uses only certain subtypes of 43B

Note: 9, 9, 9, 9 are proposed studies (not yet approved or funded)

Finally, as each major research study is rolled out, a Practice Survey will be distributed to all METRC investigators and their partners. The primary goal of these Practice Surveys is to document variation in knowledge, beliefs, and practices among orthopaedic trauma surgeons in the United States. A secondary goal is to prospectively assess the impact of METRC consortium research projects on clinical practice.

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



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-09-20108 (METRC I)

PI/Protocol Chair: Robert O'Toole, MD

The overall goal of the FIXIT study is to compare the outcomes associated with the use of modern ring external fixators versus standard internal fixation techniques in treating severe open tibia shaft or metaphyseal fractures with or without a bone defect of any size. Primary outcomes include hospital readmission for a defined set of complications. Secondary outcomes include: infection (superficial or deep), fracture healing, limb function, pain intensity and interference, and patient reported functional outcome and quality of life. Cost of treatment (for the initial hospitalization and total one-year treatment costs) will also be ascertained, as well as patient reported satisfaction with fixation method and overall treatment.

The FIXIT Study is enrolling patients

- *4 sites approved for enrollment*
- *3 sites pending DOD approval*
- *15 sites pending local IRB approval*
- *5 sites pending IRB submission*

A secondary objective will 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.

Study design: Multicenter, phase III prospective randomized controlled trial. Patients who refuse randomization will be eligible for a prospective cohort study.

Study duration: 5 years (6 month planning, 36 month accrual, 12 month final follow-up, 6 month analysis and writing). Participants will be followed for one year from the time of definitive treatment.

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

Number of study sites: 27 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, M.D, M Zadnik, PhD, R Andersen, M.D, M Bosse, M.D, R Crichlow, M.D, CDR R Gaines, M.D, LTC J Hsu, M.D, C Jones, M.D, CDR J Keeling, M.D, S Morgan, M.D, W Obremsky, M.D, A Starr, M.D, J Sontich, M.D, D Sietsema, PhD. From the Coordinating Center: E MacKenzie PhD, L Reider, MHS, R Castillo PhD, D Scharfstein ScD.

rhBMP-2 vs. Autograft for Critical Size Tibial Defects: A multicenter, randomized trial

The pTOG Study

Sponsored by: DOD OETRP

Award Number: W8XWH-09-20108 (METRC I)

Co-PIs/Protocol Co-Chairs: Lisa Cannada, MD & Paul Tornetta, III MD

The purpose of this study is to compare the effect of recombinant human bone morphogenetic protein (rhBMP-2/ACS) versus autogenous iliac crest bone graft (ICBG) on rates of fracture healing in patients with critical size defects following tibial shaft fractures. We hypothesize that rhBMP-2 is a safe substitute for the patient's own bone in fracture healing. The primary outcome for this study is fracture union at 12 months post-injury. Secondary outcomes include infection, functional status and one year medical cost. rhBMP-2 is commercially available (Medtronic Sofamer Danek, Memphis TN). It is currently approved for use within the first 14 days in open tibia fractures treated with an intramedullary nail. The FDA has granted an Investigational Device Exemption (IDE) for use of rhBMP-2 in this study.

The pTOG Study is enrolling patients

- *3 sites approved for enrollment*
- *3 sites pending DOD approval*
- *4 sites pending local IRB approval*
- *1 site pending IRB submission*

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

Study duration: 3 years (18 month accrual, 12 month final follow-up, 6 month analysis and writing). Participants will be followed for one year from the time of bone graft.

Sample size: 50 (25 per treatment group).

Number of study sites: 11 core sites.

Principal Inclusion criteria: Patients 18-65 years old with an open diaphyseal tibia fracture with a circumferential bone defect of at least one centimeter in length compromising at least 50% of the circumference of the bone.

Protocol Committee: L Cannada, M.D, P Tornetta, III M.D, W Obremsky, M.D, M Bosse, MD, LTC R Andersen, MD. From the Coordinating Center: E MacKenzie, PhD, L Reider, MHS, D Scharfstein, ScD.

St. Elizabeth's
Medical Center
Center for
Biomedical
Research

**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-09-20108 (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. We will analyze routine tissue samples collected as part of standard care employing both standard tissue culture microbiology and modern polymerase chain reaction (PCR) technologies. PCR analyses throughout this study will utilize the Ibis T5000 Biosensor System.

Core and satellite centers are in the process of submitting the BIOBURDEN protocol to their local IRB for approval.

- *1 site approved for enrollment*
- *36 sites pending local IRB approval*

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.

Study design: Multicenter, prospective cohort study.

Study duration: 24 months (9 month enrollment period, 1 year patient follow up and 3 month data analysis period). Participants will be followed for one year after injury.

Sample size: 600.

Number of study sites: 37 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, M.D, R Seymour, PhD, A Starr M.D, T Miclau M.D, J Forsberg, LTC C Murray, M.D, G Ehrlich, PhD, D Wilson, G Russell, M.D, CDR J Toledano, M.D, A Pollak, M.D, J Wenke, PhD, J Carne, M.D, R Kreft, RN. From the Coordinating Center: R Castillo, PhD, L Reider, MHS, E MacKenzie, PhD, D Scharfstein, ScD.

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)

Co-PIs/Protocol Co-Chairs: Andrew Schmidt, MD and Michael Shuler, MD

The long-term objective of this research 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 immediate 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).

The PACS Study has been approved by the METRC Steering Committee and is currently under review by the Institutional Review Board of Johns Hopkins Bloomberg School of Public Health.

Enrollment is projected to begin by the end of 2011.

Study design: Multicenter, prospective cohort study.

Study duration: 32 months (6 month planning, 12 month accrual, 6 month final follow-up, 8 month analysis and writing). Participants will be followed for six months after injury.

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

Sample size: 200.

Number of study sites: Approximately 10 core sites.

Protocol committee: A Schmidt, MD, M Shuler, MD, M Bosse, MD, J Evans, MD, R Hayda, MD, C Jones, MD, R O'Toole, MD, T Walters, MD, J.R. Westberg. From the Coordinating Center: E MacKenzie, PhD, D Scharfstein, ScD, K Frey RN, MPH, R Castillo, PhD.

St. Elizabeth's
Medical Center
Center for
Biomedical
Research

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 purpose of this study is to compare 18 month functional outcomes and health related quality of life (HRQoL) of 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. Functional outcomes and HRQoL will be measured using well established self reported measures.

Secondary objectives of the study are to 1) compare 18 month assessments of physical impairment using objective performance measures of agility, strength/power, and speed and 2) to 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.

Study design: Multicenter, 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 six months after injury.

Sample size: 464 patients will be consented; 5% of these injuries will not meet eligibility criteria upon adjudication (n=23); approximately 32% of the eligible injuries will be amputated 6 weeks after injury (n=141); and approximately 68% will be salvaged 6 weeks after injury (n=300), 94% of whom will remain salvages by 18 months after injury (n=282).

Number of study sites: Up to 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, R Seymour, PhD, J Wenke, PhD, W Gordon MD, S Morshed, MD, W Racette CPO, G Klute, PhD, R Teasdall, MD, CDR J Toledano, M.D, T Miclau, MD, B Sangeorzan, MD, K Archer-Swygert, PhD, L Cannada, MD. From the Coordinating Center: E MacKenzie PhD, L Reider, MHS, R Castillo, PhD, D Scharfstein, ScD.

The OUTLET protocol has been approved by the METRC Steering Committee and is currently under review by the Institutional Review Board of Johns Hopkins Bloomberg School of Public Health.

Patient enrollment is expected to begin by the end of 2011.

Comparison of transtibial amputation with and without a tibia-fibula synostosis

The ERTL Study

Sponsored by: DOD CDMRP PRORP

Award Number: W8XWH-10-0090 (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 of this study are to: 1) compare the fit and the alignment of the prosthesis together with levels of comfort and satisfaction; 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.

The ERTL protocol is under development. A pilot/feasibility to evaluate an objective measure of prosthetic fit and alignment using photographs and video taken by non-prosthetists is underway.

Study design: Multicenter, 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: To be determined.

Number of study sites: Up to 35 core and satellite centers.

Principal inclusion criteria: Transtibial amputation regardless of underlying injury.

Protocol committee: M Bosse, MD, R Seymour, PhD, J Wenke, PhD, MacKenzie, W Gordon MD, S Morshed, MD, W Racette CPO, G Klute, PhD, R Teasdall, MD, CDR J Toledano, M.D, T Miclau, MD, B Sangeorzan, M.D, K Archer-Swygert, PhD, L Cannada, MD. From the Coordinating Center: E MacKenzie PhD, L Reider, MS, R Castillo PhD, D Scharfstein ScD.

St. Elizabeth's
Medical Center
Center for
Biomedical
Research

Improving Pain Management in High Energy Orthopedic Trauma: The PAIN Study

Sponsored by: DOD CDMRP PRORP

Award Number: W8XWH-10-2-0090 (METRC II)

PI/Protocol Co-Chairs: Renan C. Castillo, PhD and Srinivasa N. Raja, MD

The objective of this study is to examine the use of multimodal pharmacologic perioperative pain management for orthopaedic trauma patients. Participants will be randomized into three groups: (Group 1) standard pain management plus intravenous and oral placebo; (Group 2) standard pain management plus intravenous ketorolac and oral placebo; or (Group 3) standard pain

management plus intravenous placebo and oral pregabalin. Patients will be followed for 12 months to study readmissions for complications, and to assess pain, functional outcome, and medical costs. Our overall hypothesis is that perioperative pain management will result in improved pain control, shorter hospital stays, and lower opioid consumption, but have equivalent levels of complications as standard of care pain management.

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

Study duration: 4 years (9 month planning, 18 month accrual, 12 month final follow-up, 6 month analysis and writing). Participants will be followed for one year from the time of definitive treatment.

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

Sample size: 450 (150 per arm).

Number of study sites: Between 25 and 35 core and satellite sites.

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

The protocol for the PAIN study is currently under development.

The protocol will be submitted for review by the Johns Hopkins Bloomberg School of Public Health IRB in November, 2011 with enrollment projected for April, 2012.

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

The TCCI Study

Sponsored by: DOD CDMRP PRORP

Award Number: W8XWH-10-2-0090 (METRC II)

Protocol Co-Chairs: Ellen MacKenzie, PhD and Stephen Wegener, PhD

The overall objective of this study is to develop and evaluate the effectiveness of the Trauma Collaborative Care Intervention (TCCI) in improving outcomes following major extremity trauma.

The TCCI 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 use of clinical guidelines for the management of psychological co-morbidities and; 3) the use of a ‘Recovery Coach’ to motivate use of services and promote communication between providers and patients. Primary outcomes include: function, return to usual major activity and quality of life. Secondary outcome measures include: post traumatic stress (PTSD), depressed mood, and pain. Primary and secondary outcomes will correlate strongly with intermediate outcomes of self-efficacy, patient activation, catastrophizing, and social support.

The TCCI intervention and protocol are in the development phase, with an Advisory Committee scheduled to meet in November of 2011.

The protocol will be submitted for review at the Johns Hopkins Bloomberg School of Public Health IRB in January of 2012 with enrollment projected for June 2012.

Study design: Multicenter matched cluster design.

Study duration: 54 months (6 month planning, 6 months developing TCCI, 36 month accrual, 12 month final follow-up, 6 month analysis and writing). Participants will be followed for one year from the time of definitive treatment.

Principal Inclusion Criteria (under discussion): Ages 18 – 60 years inclusive, with traumatic extremity amputations or early amputation secondary to trauma; Grade III fractures; pelvic and acetabular fractures, knee joint fractures and knee dislocations.

Sample size: 500 (250 per arm).

Number of study sites: 10 core sites.

Protocol Committee: S Wegener, PhD, M Bosse, MD, R Crichlow, MD, A Starr, MD, R Hymes, MD, C Jones, MD, H Vallier, MD, D Sietsema, PhD, RN, From the Coordinating Center: E MacKenzie, PhD, K Frey RN, MPH, D Scharfstein ScD.

St. Elizabeth's
Medical Center
Center for
Biomedical
Research

**A Prospective Randomized Trial to Assess
PO versus IV Antibiotics
for the Treatment of Early Post-op Wound Infection
after Plate Fixation of Extremity Fractures**

The POvIV Study

Sponsored by: DOD CDMRP PRORP

Award Number: W81XWH-10-2-0133

PI/Protocol Chair: William T. Obrebsky, MD, MPH

Patients with post-operative infections routinely receive up to six weeks of intravenous antibiotic therapy following surgical debridement. However, a growing evidence base suggests oral antibiotic therapy is equally effective, results in a reduced risk of complications, and lowers medical costs. The equivalence of oral versus intravenous therapy to treat wound infection after plate fixation

of extremity fractures has not been definitively established in a randomized clinical trial. Given the cost and risks associated with outpatient intravenous antibiotic therapy, and in light of the data on bioavailability, joint and bone penetration, and efficacy of oral antibiotics, this randomized clinical trial comparing the two treatment approaches will add greatly to the body of knowledge in treating these difficult infections. The trial's primary hypothesis is that the efficacy of oral antibiotic therapy (PO) is not inferior to intravenous antibiotic therapy (IV) for the treatment of infection after fracture plate internal fixation

The POvIV protocol has been approved by the METRC Steering Committee and by the Institutional Review Board at the Johns Hopkins Bloomberg School of Public Health.

Patient enrollment is expected to begin November, 2011.

Study design: Phase III randomized controlled clinical trial.

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

Sample size: 600 (300 per arm).

Number of study sites: 35-40 core and satellite sites.

Principal Inclusion criteria: Patients with long bone fractures (femurs, tibias, fibulas of the legs, and humeri, radii, ulnas of the arms) treated with a plate that will be retained until union, and diagnosed with a wound infection within six weeks of definitive fixation.

Protocol committee: W Obrebsky, MD, MPH, K Archer, PhD, DPT, LTC C Murray, MD, P Tornetta, III, MD, M Bosse, MD, A Schmidt, MD, J Anglen, MD, CDR J Keeling, MD, S Morshed, MD, MPH, T Miclau, MD, T. Talbot, MD, MPH. M Fleming, MD. From the Coordinating Center: R Castillo PhD, K Frey RN, MPH, D Scharfstein ScD., E MacKenzie, PhD

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

The APS Study

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

The treatment of high-energy military fractures continues to result in poor outcomes and be associated with high rates of infection. Local antibiotic delivery systems associated with fracture hardware have the potential to reduce complications by lowering infection rates in these patients.

Although there is strong theoretical and animal study data as well as some promising preliminary clinical data regarding the use of local antibiotics to reduce infection, it is not yet clear that Antibacterial Plate Sleeves will perform better than treatment without Antibacterial Plate Sleeves in a rigorous head-to-head clinical trial. Our hypothesis is that the use of Antibacterial Plate Sleeves for fractures at high risk for infection will reduce infection rates and therefore improve outcomes compared to standard treatment. The results of this trial have potential to reduce surgical site infection in both the military and civilian patients, and improve patient outcomes from these potentially devastating injuries.

Animal studies are underway and required for an FDA IND application (target date for submission is April 2012).

Patient enrollment is expected to begin November of 2012.

Study design: Phase III randomized controlled multicenter trial.

Study duration: 4 years (12 months planning and regulatory approval, 18 month accrual, 12 month final follow-up, 6 month analysis and writing). Participants will be followed for 12 months.

Sample size: 800 (400 per arm).

Number of study sites: Between 25 and 35 core and satellite sites.

Principal Inclusion criteria: Tibial plateau and pilon fractures initially treated in a staged fashion and then treated definitively with plate and screw fixation more than 5 days later after swelling has resolved; and calcaneus fractures initially treated in a splint or with limited percutaneous fixation or both, and then definitively more than 5 days later with plate and screw fixation after swelling has resolved.

Protocol committee: R O'Toole, MD, M Joshi, MD, M Zadnik Newell, PhD, D J Hak, MD, MBA, D Chan, MD, D Tsukayama, MD, J Langford, MD, D Sietsema, PhD, RN, Z Roberts, MD, N Rao, MD, H Mir, MD, LTC J Hsu, MD, M Graves, MD, M Bosse, MD. From the Coordinating Center: R Castillo PhD, E MacKenzie PhD, D Scharfstein ScD.

St. Elizabeth's
Medical Center
Center for
Biomedical
Research

Multicenter Investigation of the Mechanical Determinants of Post-Traumatic Osteoarthritis

The PTOA Study

Sponsored by: National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

Award Number: 1R21AR061808-01

PI/Protocol Co-Chairs: Lawrence Marsh, M.D. and Donald D Anderson, PHD

A growing body of evidence supports the theory that the intensity of the original joint trauma (injury severity) is one of the most important factors contributing to post-traumatic osteoarthritis (PTOA). Colleagues at University of Iowa have developed techniques to measure the fracture severity and validated them in surrogate bone specimens, cadavers, and in an initial patient series. The severity metric correlates strongly with PTOA development. In this multicenter pilot and feasibility study, we will eliminate an important barrier to improving treatment of articular fractures and subsequently decreasing the burden of PTOA. Mechanical metrics of acute injury severity and of 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.

The PTOA study will be conducted in tandem with the PAIN study, taking advantage of common patient populations and outcomes. The combined protocols will be submitted for review to the Johns Hopkins Bloomberg School of Public Health IRB in November, 2011 with enrollment projected to

Study design: Multicenter, prospective cohort study.

Study duration: 45 months (9 month planning, 18 month accrual, 12 month final follow-up, 6 month analysis and writing). Participants will be followed for one year from the time of definitive treatment.

Sample size: 150.

Number of study sites: Between 25 and 35 core and satellite sites.

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

Protocol committee: L Marsh, MD, D Anderson, PhD, G Russell, MD, C Jones, MD, T Higgins, MD, MAJ B Goff, DO, H Vallier, MD, B Sangeorzan, MD, P Tornetta, III, MD, D Hak, MD. From the Coordinating Center: R Castillo PhD, K Frey RN, MPH, D Scharfstein ScD, E MacKenzie, PhD.



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. Three 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 (two from DOD CDMRP and one from NIH NIAMS) 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 below.



Overview of 6-Year Budget - METRC Coordinating Center

	METRC 1	METRC 2	University of Maryland PRORP	Vanderbilt University PRORP	University of Iowa R21
Personnel - Coordinating Center	3,135,912	4,547,195	309,725	572,502	57,135
Travel - CC and Sites	219,036	663,650	14,400	19,800	
Other	235,442	405,189	15,622	10,062	4,060
DSMB Consultants (incl. travel)	219,649	453,635	22,500	13,500	
Project Specific Costs	375,000	2,941,858	3,375	85,176	
Core Civilian Centers					
Direct Costs (for PIs and RCs)	6,505,639	10,040,449			
Indirect Costs to Centers	2,950,823	4,737,484			
Patient Enrollment Costs	1,755,000	3,296,000	1,440,000*	1,380,000*	75,000*
Core MTF Centers					
Direct Costs	2,243,281	1,659,333			
IDC at 20% to Subcontractor	446,413	330,207			
Satellite Center Enrollment Costs					
Patient Enrollment Costs	735,000	925,000			
Total Direct Costs	18,821,195	30,000,000	1,805,622	2,081,040	136,195
IDC on the Direct Costs (IDC to JHU)	2,678,425	8,657,995	117,731	225,736	87,165
Total Award	21,499,620	38,657,995	1,923,353	2,306,776	223,360
* These amounts may be used to support patient enrollment either core or satellite centers					



Looking Forward

Next year will be an exciting year for METRC. All currently funded projects will be in the field and we will begin to realize the full potential of the Consortium.

In addition to assuring that studies are rolled out in a timely manner, we will focus attention on the following activities:

- We will fully implement a comprehensive data quality assurance and site monitoring program to ensure high quality data and compliance with regulatory requirements;
- The Consortium will initiate a quarterly newsletter targeted to members of the Consortium and its sponsors;
- The public face of the website will be enhanced to provide resources for study participants and their families, including educational materials, links to appropriate web resources, and research updates.

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

- ✓ Compare the performance of a new custom energy-storing ankle foot orthosis (AFO), the Intrepid Dynamic Exoskeletal Orthosis (IDEO), with the standard of care typically received by limb salvage patients (PI: LTC J Hsu, MD);
- ✓ Evaluate (within the context of an observational study) different types of bone graft protocols for the treatment of segmental defects of long bones 1-5 cm compromising at least 50% of the circumference of the bone (PI: W Obremskey, MD, MPH);
- ✓ Evaluate the effects of the antioxidant n-acetylcysteine (NAC) and the recently developed erythropoietin (EPO)-derived peptide ARA290 to forestall the development of post-traumatic osteoarthritis (PTOA) in patients with intra-articular tibial pilon fracture (PI: L Marsh, MD);
- ✓ Determine if high dose perioperative oxygen affects the rate of surgical site infection for fractures at high risk of infection (PI: R O'Toole, MD);
- ✓ Evaluate the safety and efficacy of an antibiotic-loaded chitosan sponge delivery system used adjunctively for the prevention of infections in open fractures and severe extremity wounds and to compare this delivery system against the current standard of care (PI: M Bosse, MD).

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

TABLE A

Participating Sites

MILITARY TREATMENT FACILITIES

San Antonio Military Medical Center, BAM

Principal Investigator: LTC Joseph R. Hsu, MD

Walter Reed National Military Medical Center, WRD

Principal Investigator: LTC Wade T. Gordon, MD

MAJ Wade T. Gordon, MD

Naval Medical Center Portsmouth, NPM

Principal Investigator: LCDR Robert Gaines, 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, TGH

Principal Investigator: Roy W. Sanders, MD

Hennepin County Medical Center / Regions Hospital, HCM

Principal Investigators: Andrew H. Schmidt, MD & Peter A. Cole, MD

LAC + USC Medical Center, LAC

Principal Investigator: Jackson Lee, MD

MetroHealth Medical Center, MET

Principal Investigator: Heather A. Vallier, MD

Orlando Regional Medical Center, ORL

Principal Investigator: Joshua R. Langford, MD

OrthoIndy / Methodist Hospital, MTH

Principal Investigator: Renn J. Crichlow, 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, SLU

Principal Investigator: Lisa K. Cannada, MD

Trauma Research, LLC & HealthOne Swedish Medical Center, SWE

Principal Investigator: Steven J. Morgan, 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: Robert A. McGuire, MD

University of Oklahoma Medical Center, UOK

Principal Investigator: David Teague, MD

University of Texas Southwestern Medical Center, UTX

Principal Investigator: Adam J. Starr, MD

University of Washington / Harborview Medical Center, UWA

Principal Investigator: Bruce J. Sangeorzan, MD

UT Health: The University of Texas Health Science Center at Houston, HOU

Principal Investigator: Milan K. Sen, MD

Vanderbilt University Medical Center, VMC

Principal Investigator: William T. Obremskey, MD, MPH

Wake Forest University Baptist Medical Center, WFU

Principal Investigator: Robert D. Teasdale, MD

SATELLITE CENTERS

Barnes-Jewish Hospital at Washington University, BJH

Principal Investigator: William M. Ricci, MD

Cooper University Hospital, CUH

Principal Investigator: Robert F. Ostrum, MD

Duke University Hospital, DUK

Principal Investigator: Robert D. Zura, MD

Emory University, EMU

Principal Investigator: William M. Reisman, MD

Greenville Memorial Hospital, GHS

Principal Investigator: Kyle J. Jeray, MD

Inova Fairfax Hospital, IFH

Principal Investigator: Robert A. Hymes, MD

Louisiana State University, LSU

Principal Investigator: Peter C. Krause, MD

Loyola University Medical Center, LOY

Principal Investigator: Michael Stover, MD

Medical University of South Carolina, MSC

Principal Investigator: Langdon A. Hartsock, MD, FACS

New York University Hospital for Joint Diseases, NYU

Principal Investigator: Kenneth A. Egol, MD

Northshore University Health System, NSU

Principal Investigator: TBD

Ohio State University Medical Center, OSU

Principal Investigator: Laura Phieffer, MD

Rhode Island Hospital, Brown University, RIH

Principal Investigator: Roman A. Hayda, MD

Texas Tech University Health Sciences Center, ELP

Principal Investigator: Amr A. Abdelgawad, MD

University of Kentucky, UKY

Principal Investigator: Brandon T. Bruce, MD

University of Massachusetts Medical Center, UMA

Principal Investigator: Judith A. Siegel, MD

University of Michigan Hospital, UMI

Principal Investigator: James A. Goulet, MD

University of Missouri/University Hospital, UMO

Principal Investigator: Gregory J. Della Rocca, MD, PhD

University of Pennsylvania, PEN

Principal Investigator: Samir Mehta, MD

University of Pittsburgh, PIT

Principal Investigator: Andrew R. Evans, MD

University of Rochester, ROC

Principal Investigator: John T. Gorczyca, MD

University of Texas Health Science Center, San Antonio, SAN

Principal Investigator: Animesh Agarwal, MD

University of Utah, UUT

Principal Investigator: Thomas Higgins, MD

University of Virginia Medical Center, UVA

Principal Investigator: David B. Weiss, MD



TABLE B

Staff of the Coordinating Center

Staff of the Coordinating Center

Ellen J. MacKenzie, PhD, Director

Renan Castillo, PhD, Deputy Director

Daniel O. Scharfstein, ScD, Principal Biostatistician

Gregory de Lissovoy, PhD, MPH, Principal Economist

CORE: Informatics and Biostatistics

Anthony R. Carlini, MS, Director for Informatics & Biostatistics

Andre Hackman, Senior Programmer

Steve Samudrala, MS, Programmer Analyst

Brian Dyer, Programmer

Chanen S. Chavis, Research Assistant

CORE: Protocol Development and Implementation

Lisa Reider, MHS, Director for Protocol Development, Implementation & Monitoring

Katherine Frey, RN, MPH, MS, Associate Director for Protocol Development, Implementation & Monitoring

Lauren Allen, MA, Study Manager

Susan Collins, MSc, Study Manager

Marcie Maichle, MS, Study Manager

Payal Verma, MPH, Study Manager

CORE: Administration and Regulatory Affairs

Rachel Holthaus, MS, CIP, Director, Administration & Regulatory Affairs

Cathy Epstein, Administrative Assistant

Tracy Russo, Financial Manager

TABLE C

Participating Centers

Site Participation and Status by Study Data as of October 1, 2011

*Indicates Study Protocol Under Development

Participation Confirmed
 NOT participating
 Participation Pending

	Registry	pTOG <small>*only 11 centers required</small>	FIXIT	BIOBURDEN	POVIV	PACS	OUTLET	APS*	ERTL*	PAIN*	TCCI*	PTOA*
CORE Sites												
BMC	ENR	DOD	LOC	PRE								
CMC	ENR	ENR	ENR	ENR								
DHA	ENR	PRE	PRE	PRE								
HCM	ENR		ENR	PRE								
HOU	ENR		DOD	PRE								
LAC	ENR			PRE								
MET	ENR		LOC	PRE								
MTH	ENR		LOC	PRE								
ORL	ENR		DOD	PRE								
PSU	ENR		LOC	PRE								
RYD	ENR		ENR	PRE								
SPC	ENR	DOD	PRE	PRE								
STL	ENR	ENR	LOC	PRE								
SWE	PRE											
TGH	ENR	LOC	LOC	PRE								
UIA			LOC	PRE								
UMD	ENR		ENR	PRE								
UMN	ENR			PRE								
UMS	ENR		LOC	PRE								
UOK	ENR	DOD		PRE								
USF	ENR	ENR	LOC	PRE								
UTX	ENR		PRE	PRE								
UWA	ENR	DOD		PRE								
VMC	ENR	LOC	LOC	PRE	PRE							
WFU	ENR		DOD	PRE								

For participating sites (confirmed or pending): **PRE** = site is preparing submission to local IRB; **LOC**= Local IRB approval is pending; **DOD** = DOD approval of site is pending; **ENR**= site is approved for enrollment. Cell is blank if master protocol is still under review.

Site Participation and Status by Study Data as of October 1, 2011

*Indicates Study Protocol Under Development

Participation Confirmed
 NOT participating
 Participation Pending

	Registry	pTOG <small>*only 11 centers required</small>	FIXIT	BIOBURDEN	POVIV	PACS	OUTLET	APS*	ERTL*	PAIN*	TCCI*	PTOA*
Military Treatment Sites												
BAM	ENR	LOC	LOC	PRE								
WRD	DOD		LOC	ENR								
NPM	DOD		LOC	PRE								
NSD	DOD		PRE	PRE								
Satellite Centers												
BJH												
CAR												
CUH												
DUK			LOC	PRE								
ELP			LOC	PRE								
GHS												
IFH				PRE								
JPS												
LSU				PRE								
LOY												
MSC												
NYU												
NSU												
OSU												
PEN												
PIT												
RIH				PRE								
ROC				PRE								
SAN			PRE	PRE								
UKY				PRE								
UMA												
UMI												
UMO												
UUT				PRE								
UVA												

For participating sites (confirmed or pending): **PRE** = site is preparing submission to local IRB; **LOC**= Local IRB approval is pending; **DOD** = DOD approval of site is pending; **ENR**= site is approved for enrollment. Cell is blank if master protocol is still under review.