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<b>14. ABSTRACT</b> The Major Extremity Trauma and Rehabilitation Consortium (METRC) consists of a network of clinical centers and one data-coordinating center that work together with the DoD to conduct multi-center clinical research studies. The goal of the 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. Funding for METRC has helped us to develop and sustain the data-coordinating center, establish the network of sites conducting METRC research studies, facilitate ongoing training for studies and support study specific research requirements.						
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## 1. INTRODUCTION:

The Major Extremity Trauma and Rehabilitation Consortium (METRC) consists of a network of clinical centers and one data-coordinating center that work together with the military to conduct multi-center clinical research studies. The goal of the 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. Funding for METRC has helped us develop and sustain the data-coordinating center, establish the network of sites for conducting METRC research studies, and conduct specific research studies in response to the gaps DoD has identified in orthopaedic trauma research. Initial funding for METRC was received through two cooperative agreements, referred to as METRC 1 and METRC 2. In 2016, METRC received a third consortium award- METRC 3- and was approved to conduct an additional 5 studies (this progress report focuses on METRC 3 activities):

- **PRECISE:** A Multi-Center, Prospective Observational Study to Evaluate the Use of Patient-Specific Precision Injury Signatures to Optimize Orthopaedic Interventions in Multiply Injured Patients.
- **EMS-BinD:** Early Mechanical Stabilization and Bleeding Disruption of the Pelvic Ring: A Multi-Center, Prospective Observational Study
- **Alter-G:** Early Advanced Weight Bearing for Peri-Articular Knee and Pilon Injuries: An RCT Using the Anit-Gravity Treadmill
- **CBPT:** Improving Recovery after Orthopaedic Trauma: Cognitive Behavioral Based Physical Therapy
- **LTE:** Long-Term Consequences of Major Extremity Trauma: A Pilot Study

## 2. KEYWORDS:

Clinical research consortium, extremity war injuries, trauma related outcomes, orthopaedic outcomes research

## 3. ACCOMPLISHMENTS:

- **What were the major goals of the project?**

### **Study 1: Measuring Patient Specific Injury and Progression of Immunologic Response to Optimize Orthopaedic Interventions in Multiply Injured Patients (PRECISE), PI: McKinley**

**Study 1 Specific Aims:** (1) Measure patient-specific indices that quantify injury and immunologic response to injury; (2) Evaluate the impact of surgical magnitude on patient specific physiologic and immunologic biomarkers; (3) Using patient-specific indices that quantify injury and response to injury, develop surgical decision rules that optimize clinical outcomes. **Patient Population:** Multiply injured patients 18-55 years of age requiring full trauma activation in the ER with a qualifying axial or appendicular orthopaedic injury.

	<b>Timeline</b>	<b>Status</b>
<b>Major Task 1: Study Initiation</b>	Months	
Subtask 1: Finalize master protocol	8-16	Complete
Subtask 2: Develop case report forms (CRFs) for data capture, program and pilot test REDCap	17-19	Complete
Subtask 3: Obtain initial IRB approval at JHSPH and USAMRMC	19-23	Complete
Subtask 4: Distribute approved protocol and obtain IRB approval at all participating sites	22-24	Complete
Subtask 5: USAMRMC Human Research Protections Office review and approval of site-specific IRB-approved human use documents	24-28	Complete
<i>Milestone Achieved: Local IRB approval at METRC sites and HRPO</i>	28	Complete
<b>Major Task 2: Training Research Staff</b>		
Subtask 1: Develop and conduct training for Research Coordinators on procedures for enrolling patients within first 48 hours of admission, collecting and shipping blood samples, and data collection procedures	19-22	Complete
Subtask 2: Certify sites to begin screening and enrolling patients	24-28	Complete

Subtask 3: Conduct study initiation calls with each site	24-28	Complete
<i>Milestone Achieved: Research Staff Trained</i>	28	Complete
<b>Major Task 3: Conduct Study</b>		
Subtask 1: Clinical site Research Coordinators will screen and enroll 400 eligible study patients. Coordinators will enter data collected on paper case report forms into the REDCap database and serum samples will be shipped to the core lab.	24-41	Ongoing
Subtask 2: Generate and distribute monthly enrollment and follow-up reports; provide ongoing training and support to address problems with enrollment and follow-up as they are identified	30-47	Ongoing
Subtask 3: Generate and distribute data quality reports to monitor data completeness; check for errors and inconsistencies	24-47	Ongoing
<i>Milestone Achieved: Patients enrolled</i>	41	Ongoing
<i>Milestone Achieved: All laboratory data analyzed</i>	41	Ongoing
<b>Major Task 4: Data Analysis and Report Writing</b>		
Subtask 1: Develop final analysis files	40-48	Not Started
Subtask 2: Conduct analysis and write final reports and peer-reviewed publications	48-60	Not Started
Subtask 3: Disseminate results- publication in peer reviewed journals and presentation at professional and scientific meetings	48-60	Not Started
<i>Milestone Achieved: Report findings from final analysis</i>	60	Not Started

**Study 2: Early Advanced Weight Bearing for Peri-articular Knee and Pilon Injuries: an RCT using the Anti-Gravity Treadmill (Alter-G), PI: Stinner**

<b>Study 2 Specific Aims:</b> (1) To compare functional outcomes and return to usual major activities between patients randomized to receive the intervention versus standard of care; (2) to compare patterns of recovery in range of motion and strength between; and (3) to compare performance in 4 domains of physical function- speed, power, strength, and agility. <b>Patient Population:</b> Adults ages 18-55 with periarticular fractures about the knee or distal tibia (pilon) fractures treated with ORIF (plate) for whom there are no established contra-indications that would preclude randomization to early or delayed weight bearing.		
	<b>Timeline</b>	<b>Status</b>
<b>Major Task 1: Study Initiation</b>	Months	
Subtask 1: Finalize master protocol	21	Complete
Subtask 2: Develop case report forms (CRFs) for data capture, program and pilot test REDCap	21-22	Complete
Subtask 3: Obtain initial IRB approval at JHSPH and USAMRMC	22-23	Complete
Subtask 4: Distribute approved protocol and obtain IRB approval at all participating sites	23-24	Complete
Subtask 5: USAMRMC Human Research Protections Office review and approval of site-specific IRB-approved human use documents	23-24	Complete
<i>Milestone Achieved: Local IRB approval at METRC sites and HRPO</i>	24	Complete
<b>Major Task 2: Training Research Staff</b>		
Subtask 1: Develop and conduct training for Research Coordinators on procedures for enrolling patients, data collection, and maintaining good follow-up	24	Complete
Subtask 2: Develop and conduct training for physical therapists on the standardized 10 week therapy protocol	24	Complete
Subtask 3: Certify sites to begin screening and enrolling patients	24	Complete
Subtask 4: Conduct study initiation calls with each site	24	Complete
<i>Milestone Achieved: Research Staff Trained</i>	24	Complete
<b>Major Task 3: Conduct Study</b>		
Subtask 1: Clinical site Research Coordinators will screen and enroll 200 eligible study patients. Coordinators will enter data collected on paper case report forms into the REDCap database.	24-48	Complete
Subtask 2: Generate and distribute monthly enrollment and follow-up reports; provide	24-48	Ongoing

ongoing training and support to address problems with enrollment and follow-up as they are identified		
Subtask 3: Generate and distribute data quality reports to monitor data completeness; check for errors and inconsistencies	24-60	Ongoing
<i>Milestone Achieved: All patients enrolled</i>	48	Ongoing
<i>Milestone Achieved: All patients followed</i>	60	Ongoing
<b>Major Task 4: Data Analysis and Report Writing</b>		
Subtask 1: Develop final analysis files, conduct analysis and write final reports and peer-reviewed publications	60	Not Started
Subtask 2: Disseminate results- publication in peer reviewed journals and presentation at professional and scientific meetings	60	Not Started
<i>Milestone Achieved: Report findings from final analysis</i>	60	Not Started

**Study 3: Improving Pain and Function Following Orthopaedic Trauma: A Cognitive-Behavioral Based Physical Therapy Approach (CBPT), PI: Archer**

**Study 3 Specific Aims:** (1) To determine the efficacy of the CBPT program for improving outcomes; (2) to determine whether changes in pain catastrophizing, fear of movement, and self-efficacy at 6 months are associated with improvement in outcomes; (3) to determine whether subgroups of service members and civilians are more likely to benefit from the CBPT Program. **Patient Population:** Adults ages 18-60 who are having surgical treatment for an orthopaedic injury to the lower-extremity and have psychosocial risk factors for poor outcomes.

	<b>Timeline</b>	<b>Status</b>
<b>Major Task 1: Study Initiation</b>	Months	
Subtask 1: Finalize master protocol	6-12	Complete
Subtask 2: Develop case report forms (CRFs) for data capture, program and pilot test REDCap	9-13	Complete
Subtask 3: Obtain initial IRB approval at JHSPH and USAMRMC	14-18	Complete
Subtask 4: Distribute approved protocol and obtain IRB approval at all participating sites	19-23	Complete
Subtask 5: USAMRMC Human Research Protections Office review and approval of site-specific IRB-approved human use documents	21-24	Complete
<i>Milestone Achieved: Local IRB approval at METRC sites and HRPO</i>	24	Complete
<b>Major Task 2: Training Research Staff*</b>		
Subtask 1: Conduct training of the MTF therapist on administering the intervention to military patients (civilian therapists have already received training)	-- **	Complete
Subtask 2: Develop and conduct training for Research Coordinators on procedures for screening and enrolling patients; procedures for data collection and maintaining good follow-up	19-22	Complete
Subtask 3: Certify sites to begin screening and enrolling patients	21-24	Complete
Subtask 4: Conduct study initiation calls with each site	20-24	Complete
<i>Milestone Achieved: Research Staff Trained</i>	24	Complete
<b>Major Task 3: Conduct Study</b>		
Subtask 1: Clinical site Research Coordinators will screen and enroll 320 eligible study patients. Coordinators will enter data collected on paper case report forms into the REDCap database.	22-36	Complete
Subtask 2: Study therapist will administer treatment	23-40	Complete
Subtask 3: Generate and distribute monthly enrollment and follow-up reports; provide ongoing training and support to address problems with enrollment and follow-up as they are identified	22-48	Complete
Subtask 3: Generate and distribute data quality reports to monitor data completeness; check for errors and inconsistencies	22-48	Complete
<i>Milestone Achieved: All patients enrolled</i>	36	Complete
<i>Milestone Achieved: All patients followed</i>	48	Complete
<b>Major Task 4: Data Analysis and Report Writing</b>		

Subtask 1: Develop final analysis files, conduct analysis and write final reports and peer-reviewed publications	46-60	Ongoing
Subtask 2: Disseminate results- publication in peer reviewed journals and presentation at professional and scientific meetings	46-60	Not Started
<i>Milestone Achieved: Report findings from final analysis</i>	60	Not Started

\*\* This subtask was on hold due to the low numbers of military participants and ultimately determined to be not applicable to the study.

#### **Study 4: Early Mechanical Stabilization and Bleeding in Disruption of the Pelvic Ring (EMS-BinD), PI: Gary**

<b>Study 4 Specific Aims:</b> Among patients with Young-Burgess APC 2 and 3, LC-3, vertical shear, and combined mechanism (Tile B and C) injury patterns, (1) determine if longer time to application of CPC increases need for a defined set of interventions (resuscitation with blood products, number of ventilator days, the need for angioembolization and/or pre-peritoneal pelvic packing and/or REBOA) and mortality; (2) determine if application of CPC prior to definitive hospitalization results in decreased need for a defined set of interventions and mortality; and (3) set the stage for the design and implementation of future randomized clinical trials of the use of adjuvant resuscitation approaches to improve outcomes in this patient population. <b>Patient Population:</b> Adult patients with severe high-energy pelvic ring disruptions (OTA codes 61-B and 61-C) who arrive to a level 1 trauma center within 6 hours of injury.		
	<b>Timeline</b>	<b>Status</b>
<b>Major Task 1: Pilot study</b>	Months	
Subtask 1: Develop pilot protocol	3-5	Complete
Subtask 2: Develop case report forms (CRFs) for data capture, program and pilot test REDCap	3-5	Complete
Subtask 3: Obtain initial IRB approval at JHSPH and USAMRMC	6-7	Complete
Subtask 4: Distribute approved protocol and obtain IRB approval at all participating sites	8-10	Complete
Subtask 5: Clinical site Research Coordinators review records for eligible study patients; abstract data	9-14	Complete
Subtask 6: Generate and distribute data quality reports to monitor data completeness; check for errors and inconsistencies	9-16	Complete
Subtask 7: Analyze pilot study data	16-23	Complete
Subtask 8: Generate manuscript based on pilot study data	24-30	Complete
<i>Milestone Achieved: Preliminary retrospective pilot results inform prospective study design</i>	20	Complete
<b>Major Task 2: Study Initiation</b>		
Subtask 1: Finalize master protocol	23-24	Complete
Subtask 2: Develop case report forms (CRFs) for data capture, program and pilot test REDCap	23-25	Complete
Subtask 3: Obtain initial IRB approval at JHSPH and USAMRMC	23-25	Complete
Subtask 4: Distribute approved protocol and obtain IRB approval at all participating sites	25-26	Ongoing
Subtask 5: USAMRMC Human Research Protections Office review and approval of site-specific IRB-approved human use documents	25-26	Ongoing
<i>Milestone Achieved: Local IRB approval at METRC sites and HRPO</i>	26	Ongoing
<b>Major Task 3: Training Research Staff</b>		
Subtask 1: Develop and conduct training for Research Coordinators on procedures for screening patients in the ED, collecting data from the EMS and ED flow sheets and, when applicable, obtaining autopsy data, best practices for contacting EMS providers to obtain missing data, and consenting patients or LARs.	27-28	Complete
Subtask 2: Certify sites to begin screening and enrolling patients	27-28	Complete
Subtask 3: Conduct study initiation calls with each site to ensure procedures are in place to allow access to EMS and autopsy data	27-28	Complete
<i>Milestone Achieved: Research Staff Trained</i>	28	Complete
<b>Major Task 4: Conduct Study</b>		
Subtask 1: Clinical site Research Coordinators will screen and enroll eligible study	27-52	Ongoing

patients		
Subtask 2: Generate and distribute monthly enrollment and follow-up reports; provide ongoing training and support to address problems with enrollment as they are identified	27-52	Ongoing
Subtask 3: Generate and distribute data quality reports to monitor data completeness; check for errors and inconsistencies	28-58	Ongoing
Subtask 4: Generate and submit request for SSDI data to evaluate 30-day mortality of enrolled patients	56	Not Started
<i>Milestone Achieved: All patients enrolled</i>	52	Not Started
<b>Major Task 5: Feasibility Study</b>		
Subtask 1: Develop data presentation profiles of cases to demonstrate variability in patterns of care	46-52	Not Started
Subtask 2: Convene protocol committee to provide ratings of equipoise and willingness to randomize selected cases to alternative treatments	52-54	Not Started
<i>Milestone Achieved: Document acceptability and equipoise of surgeons regarding adjuvant resuscitation approaches</i>	54	Not Started
<b>Major Task 6: Data Analysis and Report Writing</b>		
Subtask 1: Develop final analysis files	52-58	Not Started
Subtask 2: Conduct analysis and write final reports and peer-reviewed publications	54-60	Not Started
Subtask 3: Disseminate results- publication in peer reviewed journals and presentation at professional and scientific meetings	54-60	Not Started
<i>Milestone Achieved: Report findings from final analysis</i>	60	Not Started

#### **Study 5: Follow-up of METRC Participants to Examine Secondary Health Effects and Long Term Costs (LTE), PI: Castillo**

**Study 5 Specific Aims:** (1) To define the research questions of greatest importance and formulate hypotheses that will drive the study design of the main study; (2) to pilot procedures for locating and consenting METRC participants for a long-term (3-5 years post-injury) follow-up evaluation, identifying barriers for participation and appropriate use of alternative incentives; (3) to develop and pilot the evaluation procedures to include interviews, clinical exams, performance testing, medical record retrieval, and laboratory and radiographic assessments; and (4) to prepare for the successful implementation of the main study by establishing protocols and procedures, satisfying regulatory requirements, and submitting a competitive application for funding. **Patient Population:** Participants originally enrolled in the following METRC studies: FIXIT, OUTLET, TAOS, TCCS, BIOBURDEN, PAIN, PACS, OXYGEN, VANCO, PRIORITI-MTF, and OXYGEN

	<b>Timeline</b>	<b>Status</b>
	Months	
<b>Major Task 1: Study Initiation</b>		
Subtask 1: Finalize master protocol	25-27	Complete
Subtask 2: Develop case report forms (CRFs) for data capture, program and pilot test REDCap	25-27	Complete
Subtask 3: Obtain initial IRB approval at JHSPH and USAMRMC	27-29	Complete
Subtask 4: Distribute approved protocol and obtain IRB approval at all participating sites	29-32	Ongoing
Subtask 5: USAMRMC Human Research Protections Office review and approval of site-specific IRB-approved human use documents	30-33	Ongoing
<i>Milestone Achieved: Local IRB approval at METRC sites and HRPO</i>	33	Not Started
<b>Major Task 2: Training Research Staff</b>		
Subtask 1: Develop and conduct training for Research Coordinators in developing contact files, tracing potential participants, and documenting all attempts at follow-up, as well as conducting interviews and scheduling follow-up visits	30-31	Ongoing
Subtask 2: Certify sites to begin screening and enrolling patients	30-33	Not Started
Subtask 3: Conduct study initiation calls with each site to ensure procedures in place for contacting participants and completing in-person clinical examinations	30-33	Not Started
<i>Milestone Achieved: Research Staff Trained</i>	33	Not Started
<b>Major Task 3: Conduct Study</b>		
Subtask 1: Clinical site Research Coordinators will screen and re-consent 100 eligible study	31-37	Not Started

patients, including scheduling in person appointments		
Subtask 2: Generate and distribute monthly enrollment and follow-up reports; provide ongoing training and support to address problems with enrollment and follow-up as they are identified	31-37	Not Started
Subtask 3: Generate and distribute data quality reports to monitor data completeness; check for errors and inconsistencies	32-39	Not Started
<i>Milestone Achieved: Patients complete all study related activities</i>	39	Not Started
<b>Major Task 4: Feasibility Study</b>		
Subtask 1: Obtain feedback from research staff on procedures to track and bring participants back to clinic	31-37	Not Started
<i>Milestone Achieved: Refined procedures for following patients and encouraging return for in-person clinic visit</i>	37	Not Started
<b>Major Task 4: Data Analysis and Report Writing</b>		
Subtask 1: Develop final analysis files	39-41	Not Started
Subtask 2: Conduct analysis and write final reports and peer-reviewed publications	41-48	Not Started
Subtask 3: Prepare grant submission funding long term follow-up of full METRC cohort	41-48	Not Started
<i>Milestone Achieved: Report findings from final analysis</i>	48	Not Started
<i>Milestone Achieved: Grant submission for full cohort study</i>	48	Not Started

- **What was accomplished under these goals?**

## Major Activities

### *Leadership Transition*

In October of 2020, clinical leadership of the consortium and leadership of the METRC Coordinating Center transitioned from Mike Bosse, MD and Ellen MacKenzie, PhD to Bob O'Toole, MD and Renan Castillo, PhD, respectively. In METRC's annual meeting in April 2021, the new leadership, and investigators across the consortium, took a moment to honor Dr. Bosse and Dr MacKenzie's visionary leadership and impact on the field of orthopaedic trauma research and care. Investigators were given an opportunity to express their personal appreciation; their comments were compiled into this video: <https://vimeo.com/535341121>. The password to access the video is THANKYOU.

### *COVID-19*

METRC continued to monitor the impact of the COVID-19 pandemic on research sites over the course of the project year. Nearly all sites remained fully operational and, as with the last project year, Coordinating Center operations were entirely uninterrupted. While sites all resumed research activities, with administrative work largely conducted remotely and patient-facing work conducted in person per COVID safety protocols, the overall impact of COVID was slowed enrollment due to lower patient volumes. Sites and the MCC were vigilant in ensuring that all research activities within the sites' control were continued with as much rigor and commitment as before the pandemic. Additional time due to efficiencies gained in some study logistics occurring remotely, were repurposed for data quality and data clean-up work. While there was surely an impact of COVID-19 on METRC 3 study enrollment and follow-up, each of the five projects made significant strides towards successful completion. The details of each study's progress are described below.

### *CBPT*

Enrollment into CBPT was completed during the last project year, and as anticipated, follow-up was completed this year with the final visit conducted in June 2021. A total of 325 patients were randomized into the study. Of those, 268 completed the intervention and 264 completed follow-up (81.2%).

One significant event occurred over the course of the year with regard to data collection. Data collection forms were amended to add a new "Healthcare Resources Utilization" for to capture services utilization reported on medical records through 12 months post initial hospital discharge.

The Statistical Analysis Plan was finalized and signed at the end of the project year on 9/27/2021 and the database was locked on 9/28/2021. Main results analyses commenced immediately following database lock. We expect that the main results paper will be finalized and submitted for publication within the first half of the No Cost Extension year.

### *AlterG*

Enrollment into the study concluded on September 30, 2021. At this time, a total of 80 patients were enrolled across 10 participating centers. Of the 80 patients enrolled, 2 were considered to be late ineligible and were withdrawn from the study leaving 78 eligible patients enrolled; 41 randomized to the standard of care arm and 39 randomized to the intervention arm. To date, 10 patients discontinued from the study after randomization, 21 patients completed the study and 49 patients are actively being followed.

The DoD Government Steering Committee approved the study team's request to change the sample size of the study following the annual meeting on August 16<sup>th</sup>, 2021. The sample size was changed from 200 randomized patients (based on detecting moderate differences in the PROMIS Physical Function score) to 86 patients (based on detecting minimally important differences in the KOOS and AOS scores). This modification was made because KOOS and AOS which are joint specific measures of function may be more sensitive to change and this is consistent with a similar trial conducted in Germany. The IRB approved the protocol change on September 10<sup>th</sup>, 2021. At the time enrollment concluded, we reached 94% of our target sample.

We are providing real-time data quality checks on the main study outcome measures by utilizing the tools on REDCap. A physical therapist is reviewing the clinical assessment data periodically to address any data collection errors. All the study sites are receiving a weekly report on screening, enrollment, and follow-up activities. Since the last report, data queries on all missing data have been developed and the reports are provided to the sites on the weekly basis.

### *EMS-BinD*

Overall, the EMS-BinD continues to push toward its enrollment goal of 600 participants / records. To date, 2496 records have been screened for eligibility and 549 records have been provisionally enrolled into the study. There are 21 certified sites currently screening patients and 1 additional site is currently awaiting IRB approval to participate.

There were several major developments over the past project year related to the study, including two protocol amendments, both of which were pursued with the approval of the study protocol committee. Both amendments were initiated in response to ongoing enrollment challenges and to potentially improve data quality. The first amendment added an adjudication process to ensure study eligibility. This is done through a review panel comprised of 3 fellowship trained orthopaedic surgeons that review detailed injury information as well as radiographs to verify the study injury meets the inclusion/exclusion criteria. The amendment also extended the period of screening and enrollment from 48 hours post-injury through first clinical follow up (approximately 2 weeks following injury). This change, along with some administrative and other minor adjustments to study processes provide additional time to gather the necessary information so sites could avail potentially enroll patients that may have previously "timed out" of this process

The second amendment swapped the order of specific aims #1 and #2 based on feedback provided by the study protocol committee following the review of preliminary data and in light of sustained enrollment difficulties. The amendment also changed the study design from employing a prospective enrollment strategy to a joint prospective and retrospective approach. The inclusion of retrospective records (all of which must meet the same inclusion/exclusion criteria) was expected to help ensure the scientific goals of the study would be met without sacrificing data quality. The amendments made have helped to close the gap in the study enrollment given previous difficulties and delays. The study appears to be on track to meet its goals in the upcoming project year.

Also, during the past year, the principal investigator of this study, Dr. Joshua Gary, left his position at the University of Texas Health Science Center at Houston to become the Chief of the Orthopaedic Trauma Service at the Keck School of Medicine of the University of Southern California. This move did not affect study operations and study leadership at the Houston site was transitioned seamlessly. Dr. Gary immediately began the process (even before his official start) of helping to make USC as a new METRC participating site and they are now awaiting IRB approval to begin screening and

enrollment as soon as possible.

The plans for the next quarter center around continuing to screen and enroll patients. The final participating site will be certified during this period as well. Adjudication panel review of all provisionally enrolled records will continue. Data quality reports and data queries will be produced and addressed by participating sites in anticipation of beginning the main results analysis in the subsequent quarter.

### *PRECISE*

The PRECISE study is a multicenter prospective investigation working to develop a highly quantitative tool that defines the optimal timing for specific orthopaedic interventions to limit short and long term unwanted outcomes. The indices used to express a precision-injury signature, unique to each patient, include 1) mechanical tissue damage volume; 2) cumulative hypoperfusion; 3) immunologic response; and 4) demographics.

To this end, the study quantifies individualized injury magnitudes, individualized immunologic response profiles to injury by measuring serial changes in biomarkers during the acute phase of injury, and individualized quantities of surgical interventions. Ultimately, the precision injury signature unique to each patient can be used to inform intervention choices and titration.

Over the past year, the PRECISE protocol was amended to clarify the exclusion based on the prohibition of enrollment of participants with an unresolved Glasgow Coma Scale Scores (GCS). Also, Spanish speakers were added to the study population and the time to consent participants was extended from within 48 hours of enrollment to the end of the index hospitalization.

The PRECISE protocol paper was also completed. It thoroughly describes the complex measurements in this study, which will serve as a reference for future publications. This paper will be published in the Jan 2021 *Journal of Orthopaedic Trauma* METRC supplement.

### *Long-Term Effects*

During the past year, the Long Term Effects protocol was finalized and we received master study approval by the Johns Hopkins sIRB. Due to the timing of the single IRB provision of the revised Common Rule taking effect, the LTE study is the only one of the five METRC studies which was required to use a single IRB. The master protocol is currently under DoD HRPO review. Two sites have received local IRB approval and have submitted their pSite applications to the sIRB. One site has been approved and one is currently under review. Two additional sites are undergoing local IRB review.

The Case Report Form portfolio was also finalized, and the REDCap database was piloted and tested. Data sets of potentially eligible past participants have been generated and prepared for the study teams to use upon regulatory approval. These datasets constitute partial screening records. Trainings on completing the screening records, contacting participants, and coordinating and completing in-clinic visits have commenced.

## **Specific Objectives**

Nothing to report.

## **Significant Results, Key Outcomes**

Nothing to report.

## **Other Achievements**

### *Updates Pertaining to METRC 3 Standing Committees*

#### Publications Committee

The activity of the Publications Committee over the past year was primarily centered around prospectively reviewing METRC papers. Nearly all of these papers reported results of earlier METRC studies. Recently published papers include the VANCO Main Results paper (JAMA Surgery); the Prevent Clot Protocol Paper (JBJS); the OUTLET Main Results paper

(JBJS); a paper reporting the impact of severe distal tibia, ankle, and mid to hindfoot trauma on meeting physical activity guidelines 18 months after injury (Archives of PM&R); and a paper reporting the economic impact of work productivity loss following lower extremity trauma (JBJS- accepted, e-pub pending).

In addition to the recently published papers, the Publications Committee reviewed the main results papers for 4 other earlier METRC studies- FIXIT (RCT), TCCS, OXYGEN, and RetroDEFECT. These papers are currently under review at the journals; FIXIT and OXYGEN were submitted to JBJS and TCCS and RetroDEFECT were submitted to JOT.

Another major undertaking for the Publications Committee this past year was reviewing 6 papers which will be published in a supplement to the JOT in January of 2022. These papers included the protocol papers for 4 of the METRC 3 studies- CBPT, AlterG, PRECISE, and LTE. The Supplement will also include an implementation paper related to the STREAM study and a methods paper related to the PACS Study; both of these studies were earlier METRC projects.

The Publications Committee reviewed and approved 2 abstracts for the 2021 Orthopaedic Trauma Association (OTA) Annual Meeting and 6 abstracts for the 2022 Extremity War Injury Symposium (EWI). Both of the OTA abstracts were accepted and presented in October 2021. One of the abstracts presented a retrospective marginal analysis of administrative and financial data from completed METRC studies to determine the optimal number of sites to have in a prospective multicenter trial in orthopaedic trauma. The other abstract presented 12 month results from the TCCS, METRC 2 study. The 6 abstracts submitted to EWI included the FIXIT RCT results, OXYGEN main results, POVIV main results, ProFIT validation, the 12 month results from the TCCS study, and an analysis of the effect of increased cumulative hypotension on early lymphoid response in blunt trauma patients with major fractures.

Finally, the Publications Committee updated the policy related to the logistics of obtaining Corporate Authorship information from Corporate Authors on primary and secondary METRC papers. The MCC will now send 3 reminders and follow-up with site PI for non-responders to the REDCap authorship surveys. Individual who do not respond after these reminders will not be included in the authorship. The MCC will continue to streamline the corporate authorship logistics so that the survey completion will be even easier and require fewer reminders.

### Science Committee

The Science Committee continued to meet periodically to review grant proposals. Four proposals were selected for support for this year's PRORP RFA. They are noted below. In addition to reviewing the grant proposals, the Science Committee facilitated discussions about new study ideas which may be appropriate for funding outside of the annual PRORP RFA.

1. Pilot Study of Role of pH in Diagnosis of ACS (PI: Schmidt, Hennepin)
2. PO versus IV antibiotics for the treatment of infected nonunion of fractures after fixation (PI: Obremskey, Vanderbilt)
3. Early Prediction of Fracture-related Infection Following At-risk Tibia Fracture (PIs: McKinley & Natoli, Indianapolis)
4. Gentamicin Coated Intramedullary Nails for the Treatment of Open Tibia Fractures – Phase II feasibility study (PI: O'Toole, Maryland)

The Science Committee also began to develop a process to assign and prioritize cross-cutting papers, ensuring that ideas are pooled appropriately and that there is broad opportunity for investigators to contribute to manuscripts.

### Emerging Investigators Committee

The EI Committee had another light year. Beyond the ad hoc assistance provided to previous year's awardees, the committee did not meet as it was decided not to fund additional rounds of EI awards. The Committee has been obtaining status updates from the awardees and will be prepared to share these updates during the next reporting period.

### Rehab Engagement Committee

The Rehab Engagement Committee has continued to act as a key advisor to the rehab-focused study teams, especially AlterG. The rehab studies have shown themselves to be logistically challenging under normal circumstances. With additional logistical pressure applied as a result of the pandemic, experts in rehab were essential in carefully evaluating

ongoing safety and likelihood of success under additional constraints. Most notably, this committee was very involved in the update to the AlterG sample size and primary outcome.

#### Data Standards Committee & Implementation & Quality Committee

Over the course of the year, the Data Standards Committee (DSC) and the Implementation & Quality Committee (IQC) made significant progress on Coordinating Center initiatives. These committees have continued to work together to address issues related to the committees' core missions, improve study development processes, and to move forward in addressing study data quality. During this past year, METRC prepared and launched 6 new studies. This formative work, combined with the data cleaning and analysis efforts of older METRC studies and prospective data cleaning of ongoing METRC studies, have provided a unique opportunity to highlight lessons learned and implement improvements to advance data quality in the next generation of METRC studies. The foundation of this work are the data dictionaries associated with all of our existing studies, which have been combined into an integrated collection of study questions, data domains and constructs and applicable study metadata. This resource continues to support the management of ongoing projects and the development of newer studies, ensuring consistency and improving efficiency in the time needed to launch a study.

Furthermore, the data dictionary work has supported a streamlined case report form (CRF) development process, embraced by the MCC and its Informatics Core. It also improves our data standardization efforts when reviewing the data requirements of a given study or as part of an "all hands" review of data collection materials prior to study initiation.

Finally, the work of the DSC and IQC is further supported by a growing and robust, state-of-the-art, automated data query system used to prospectively clean study data. The many ongoing analyses and data monitoring efforts associated with all METRC studies in turn yield additional items for consideration and review by the DSC.

The DSC and IQC expect to continue the specific activities noted above. Additionally, the DSC plans to conduct in depth reviews of several injury/fracture classification systems to develop guidance documents to help site personnel interpret questions correctly and ensure proper usage as part of studies. Finally, the committees will have an active role in developing a repository of standards for analysis, scoring of data collection instruments, and in the development of analytic data sets and related materials for release outside the MCC.

- **What opportunities for training and professional development has the project provided?**

Nothing to report.

- **How were the results disseminated to communities of interest?**

Nothing to report.

- **What do you plan to do during the next reporting period to accomplish the goals?**

We will continue to enroll into EMS-BinD, PRECISE, and LTE. We will complete follow-ups in AlterG. We will submit the main results from CBPT for publication.

#### **4. IMPACT:**

- **What was the impact on the development of the principal discipline(s) of the project?**

Nothing to report.

- **What was the impact on other disciplines?**

Nothing to report.

- **What was the impact on technology transfer?**

Nothing to report.

- **What was the impact on society beyond science and technology?**

Nothing to report.

## 5. **CHANGES/PROBLEMS:**

- **Changes in approach and reasons for change**

Please see the study-specific notes in the 'Major Activities' section above for a detailed description of significant study amendments, changes in scope of work, and the impact of COVID-19. All significant changes were first proposed to the DoD and approved prior to implementation.

- **Actual or anticipated problems or delays and actions or plans to resolve them**

We expect that we will be able to complete the 5 studies per the updated Statement of Work and by the end of the 6<sup>th</sup> Project (No Cost Extension) Year.

- **Changes that had a significant impact on expenditures**

Nothing to report.

- **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

Nothing to report.

- **Significant changes in use or care of human subjects**

Nothing to report.

- **Significant changes in use or care of vertebrate animals.**

Nothing to report.

- **Significant changes in use of biohazards and/or select agents**

Nothing to report.

## 6. **PRODUCTS:**

- **Publications, conference papers, and presentations**

Nothing to report.

- **Website(s) or other Internet site(s)**

All METRC publications and presentations are posted on the METRC website: [www.metrc.org](http://www.metrc.org).

- **Technologies or techniques**

Nothing to report.

- **Inventions, patent applications, and/or licenses**

Nothing to report.

- **Other Products**

Nothing to report.

## **7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

- **What individuals have worked on the project?**

See Appendix A – Personnel (Annual effort).

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

1. Effort support for Dr. Katherine Frey reduced from 25% to 15% for the period Oct 2020 – Sep. 2021.
2. Effort support for Dr. Lauren Allen increased from 50% to 55% for the period Oct 2020 – Sep. 2021.

**What other organizations were involved as partners?**

See Appendix B.

## **8. SPECIAL REPORTING REQUIREMENTS**

- **COLLABORATIVE AWARDS:**
- **QUAD CHARTS:**

## **9. APPENDICES:**

**Appendix A: Personnel (Yr5 - Annual)**

**METRC III**

<u>Personnel</u>	<u>Role</u>	<u>Calendar Months</u>
Ellen Mackenzie	Principal Investigator, Director	0.60
Renan Castillo	Deputy Director	2.40
Daniel Scharfstein	Lead Statistician	1.56
Richard Thompson	Statistician	6.00
Stephen Wegener	Co-Investigator	0.60
Lisa Reider	Project Director	3.00
Katherine Frey	Project Director	1.80
Lauren Allen	Operations Director	6.60
Suna Chung	Program Manager	7.20
Kevin McLaughlin		1.50
Linda Gai	Data Analyst	0.06
Rachel Zamoiski	Data Analyst	10.20
Yanjie Huang	Data Analyst	6.00
Kuladeep Sudini	Data Analyst	5.40
Jack Dagg	Data Analyst	5.40
Vadim Zipunnikov	Statistician	0.24
Susan Collins	Study Manager	7.20
Tara Joseph	Study Manager	1.08
Dana Alkhoury	Study Manager	5.40
Craig Remenapp	Study Manager	4.80
Andre Hackman	Statistician	0.84
Anthony Carlini	Project/Technical Director	8.40
Christina Owens	Research Assistant	8.40
Manisha Kumar	Financial Manager	5.40
Chris Witczak	Financial Analyst	6.00
Cathy Epstein	Administrative Coordinator	9.60
Elena Staguhn	Research Assistant	6.60
Paige Sullivan	Programmer	7.80
Lucie Wiedefeld	Research Assistant	12.00
Elias Weston Farber	Programmer	6.60
Trisha Chaffee	Program Manager	5.40
Aiden Mcdermot	Data Analyst	1.20
Virgil Demario	Research Assistant	6.00

*Sub to Utah*

*Effort reduced from 25% to 15%*  
*Effort increased from 50% to 55%*

*No longer with METRC effective 02/15/2021*

*Left METRC effective June 2021*

*Replaced Alina Grigorovich*

**Table 1. METRC 3 Participating Sites: Approval Status and Enrollment**

Code	Site Name	METRC 3 Studies			
		CBPT*	AlterG*	PRECISE	EMS-BinD
BAM	San Antonio Military Medical Center (SAMMC)	Actively Following Patients 15 screened 7 enrolled 3 randomized	Actively Screening 102 screened 5 enrolled 5 randomized Reopen Approval: 5/21/2020		Provisionally Certified 106 screened 9 enrolled Reopen Approval: 5/22/2020
BMC	Boston Medical Center				Certified
CMC	Carolinas Medical Center	Actively Following Patients 708 screened 114 enrolled 56 randomized		Actively Enrolling 229 screened 16 enrolled	Actively Enrolling 282 screened 35 enrolled Reopen Approval: 5/8/2020
HCM	Hennepin Healthcare Research Institute		Actively Enrolling 25 screened 7 enrolled 7 randomized Reopen Approval: 6/17/2020	Actively Enrolling 3 screened 2 enrolled	Actively Enrolling 10 screened 9 enrolled Reopen Approval: 6/17/2020
HOU	UT Health: The University of Texas Health Science Center at Houston Medical School	Actively Following Patients 695 screened 181 enrolled 74 randomized	Actively Enrolling 399 screened 12 enrolled 11 randomized Reopen Approval: 5/19/2020	Actively Enrolling 90 screened 22 enrolled Reopen Approval: 5/28/2020	Actively Enrolling 773 screened 112 enrolled Reopen Approval: 5/8/2020
IFH	Inova Fairfax Hospital		Actively Enrolling 140 screened 20 enrolled 20 randomized Reopen Approval: 5/7/2020		Actively Screening 30 screened 17 enrolled
MTH	Methodist Hospital	Actively Following Patients 698 screened 106 enrolled 68 randomized		Actively Enrolling 473 screened 110 enrolled Reopen Approval: 5/18/2020	Actively Enrolling 184 screened 52 enrolled Reopen Approval: 5/12/2020
NSD	Naval Medical Center San Diego		Actively Enrolling 6 screened 2 enrolled 2 randomized Reopen Approval: 6/4/2020		
PIT	University of Pittsburgh			Actively Enrolling 1 screened 1 enrolled Reopen Approval: 7/6/2020	Actively Enrolling 33 screened 32 enrolled
RYD	University of Miami Ryder Trauma Center			Withdrew from Participating	Actively Enrolling 2 screened 1 enrolled
TGH	Tampa General Hospital	Actively Following Patients 292 screened			

		55 enrolled 35 randomized			
UKY	University of Kentucky		Actively Enrolling 38 screened 15 enrolled 15 randomized Reopen Approval: 7/9/2020	Actively Enrolling 23 screened 11 enrolled Reopen Approval: 11/13/2020	
UMD	University of Maryland, R Adams Cowley Shock Trauma Center	Actively Following Patients 654 screened 106 enrolled 48 randomized		Actively Enrolling 309 screened 16 enrolled Reopen Approval: 9/14/2020	Actively Enrolling 176 screened 34 enrolled Reopen Approval: 5/11/2020
UVA	University of Virginia Medical Center		Actively Enrolling 74 screened 8 enrolled 8 randomized Reopen Approval: 5/14/2020		
UWA	University of Washington / Harborview Medical Center			Actively Enrolling 1384 screened 33 enrolled Reopen Approval: 6/9/2020	Actively Enrolling 341 screened 17 enrolled Reopen Approval: 5/27/2020
VMC	Vanderbilt University Medical Center	Actively Following Patients 601 screened 64 enrolled 42 randomized		Actively enrolling 68 screened 38 enrolled	Actively Enrolling 91 screened 55 enrolled Certified after Reopen Plan
WFU	Wake Forest University Baptist Medical Center				Actively Enrolling 132 screened 26 enrolled Reopen Approval: 6/5/2020
WRD	Walter Reed National Military Medical Center (WRNMMC)	Certified <i>No screening initiated</i>	Actively Screening 3 screened 1 enrolled 1 randomized Reopen Approval: 6/25/2020		
MET	MetroHealth Medical Center				Actively Enrolling 48 screened 22 enrolled Reopen Approval: 5/8/2020
ESK	Eskenazi Health				Actively Screening 37 screened 19 enrolled Reopen Approval: 9/22/2020
HRV	Harvard Orthopaedic Trauma Service				Actively Enrolling 18 screened 12 enrolled
PSU	Penn State University M.S. Hershey Medical Center				Actively Enrolling 5 screened 2 enrolled

UMS	University of Mississippi Medical Center				Actively Enrolling 45 screened 26 enrolled
UOK	University of Oklahoma/ OU Medical Center				Actively Enrolling 34 screened 20 enrolled
UAB	University of Alabama at Birmingham				Actively Enrolling 64 screened 30 enrolled
USF	University of California San Francisco		Actively Enrolling 64 screened 5 enrolled 5 randomized Reopen Approval: 6/18/2020		
NPM	Naval Medical Center Portsmouth		Actively Enrolling 6 screened 6 enrolled 6 randomized		