Major Extremity Trauma Research Consortium (METRC):
Streamlining Trauma Research Evaluation with Advanced Measurement:
STREAM Study

Sponsored by: National Institutes of Health National Institute of Arthritis and
Musculoskeletal and Skin Diseases
Contract Number: 1R01AR064066-01

IND# N/A
IDE# N/A

Principal Investigators/Protocol Chairs:
Renan Castillo, PhD

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Section 6.
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Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines. The Lead Principal Investigator (Protocol Chair) should sign Signature Page 1. A copy of this Signature Page 1 should be filed with the holder of the Regulatory documents and a copy should be maintained at the site.

Principal Investigator: ____________________________________________

Print/Type

Signed: ___________________________________ Date: ________________

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

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AFIRM</td>
<td>The Armed Forces institute of Regenerative Medicine</td>
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<tr>
<td>CDMRP</td>
<td>Congressionally Directed Medical Research Program.</td>
</tr>
<tr>
<td>CCCS</td>
<td>Civilian Core Clinical Sites</td>
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<tr>
<td>DOD</td>
<td>Department of Defense</td>
</tr>
<tr>
<td>DOD HRPO</td>
<td>DOD Human Research Subject Protection Office.</td>
</tr>
<tr>
<td>DOD PRORP</td>
<td>Department of Defense Peer Reviewed Orthopaedic Research Program</td>
</tr>
<tr>
<td>Master Consent Form</td>
<td>Template consent form designed for study by the MCC</td>
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<tr>
<td>Master IRB application</td>
<td>Template IRB application designed for study by the MCC</td>
</tr>
<tr>
<td>MCC</td>
<td>METRC Coordinating Center of the Consortium</td>
</tr>
<tr>
<td>MCC Study Manager</td>
<td>Principal site contact for Research Coordinators at sites</td>
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<tr>
<td>MTF Core Clinical Sites</td>
<td>Military Treatment Facilities Core Clinical</td>
</tr>
<tr>
<td>OETRP</td>
<td>Orthopaedic Extremity Trauma Research Program</td>
</tr>
<tr>
<td>PPM</td>
<td>Policy and Procedure Memorandum</td>
</tr>
<tr>
<td>SCC</td>
<td>Satellite Clinical Sites</td>
</tr>
<tr>
<td>AI</td>
<td>Site Associate Investigators.</td>
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<tr>
<td>RC</td>
<td>Site Research Coordinator</td>
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<tr>
<td>RS</td>
<td>Site Research Staff</td>
</tr>
<tr>
<td>Study Number</td>
<td>Protocol identification number</td>
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<tr>
<td>Study Principal Investigator</td>
<td>Lead Investigator on a protocol</td>
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<tr>
<td>Study Protocol Committee</td>
<td>Protocol development</td>
</tr>
<tr>
<td>REDCap</td>
<td>Research Electronic Data Capture System</td>
</tr>
<tr>
<td>USAMRMC</td>
<td>United States Army Medical Research and Material Command</td>
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PROTOCOL SUMMARY

**Title:** Streamlining Trauma Research Evaluation with Advanced Measurement (STREAM)

**Sponsor:** NIH

**Type of study:** Prospective longitudinal observational outcomes study

**Objective:** As part of the NIH Roadmap initiative, PROMIS (patient reported outcomes measurement information system) has developed tools, including item banks, short forms and computer-adaptive tests (CATs) that can help standardize measurement for many health-related quality of life domains. These PROMIS tools are being tested in large general population samples across the lifespan. The overall goal of the present study is to assess the performance and research utility of these new tools in new patient populations for future comparative effectiveness research projects. The proposed project will examine the reliability, validity and responsiveness of the PROMIS tools for clinical research following orthopaedic trauma.

**Specific Aim 1:** Examine the measurement properties of existing PROMIS CATs and item banks in patients with orthopaedic trauma. We will incorporate ten (six core and four exploratory) PROMIS short form and CATs into the longitudinal data collection of four ongoing orthopaedic trauma clinical trials and administer an expanded data collection interview at the time of their last study follow up which will be used to:

1a: Evaluate reliability and construct validity of the PROMIS CATs
1b: Compare measurement precision of the six existing item banks when applied in an orthopaedic trauma population versus the general population.
1c: Identify items from existing PROMIS item banks that function differently in our population compared with the general population.

**Specific Aim 2:** Examine the responsiveness of existing PROMIS domains in patients with orthopaedic trauma. Specifically, we will:

2a: Examine the responsiveness of PROMIS domains against expected clinical recovery in this population.
2b: Examine the responsiveness of PROMIS domains against well-defined clinical inflection points in the recovery process, such as infections, non-unions, flap failures, and other complications.
2c: Examine the responsiveness of PROMIS domains against treatment effects observed for interventions being studied in these trials, which include a psychosocial intervention, a pharmacologic intervention, and a device. These trials are being evaluated using widely used traditional outcome measurement tools.

**Specific Aim 3:** Study the integration of the PROMIS tools within the data collection infrastructure of METRC. Key feasibility components examined will be integration with our distributed electronic data capture system (REDCap), and use of the CAT technology across dozens of trauma centers and orthopaedic trauma clinics.
3a. Compare the rate of use of CAT-based assessment versus short-form data collection
3b: Compare the data completeness using existing METRC approaches, CAT and short form
PROMIS instruments
3c: Compare respondent burden using existing METRC approaches, CAT and short form
PROMIS instruments.

**Study design:** The STREAM study is a multi-center, prospective longitudinal observational
study to evaluate the reliability, validity and responsiveness of PROMIS tools in orthopaedic
trauma patients.

**Study duration:** 4 years

**Sample size:** 1,000 patients

**Number of study sites:** Up to 50 centers including Core METRC sites, MTFs, and METRC
satellite sites.

**Study population:** Patients currently enrolled in the METRC FIXIT, OUTLET, PAIN, Oxygen
and TAOS studies.

**Outcome measures:** This ancillary project to four METRC clinical trials is designed to study the
validity, reliability and responsiveness of the PROMIS tools for assessing: Ability to participate
in social roles and activities, Depression; Anxiety; Psychosocial Impact (Positive); Pain
Interference; and Physical Function. The study will also explore three additional PROMIS
domains (Sleep; Satisfaction with participation in social roles; Applied Cognition; and Emotional
Support).

**Statistical analysis:** Item response theory techniques will be used to examine whether PROMIS
item weights differ between the normative and orthopaedic trauma populations. Various
analytical techniques will be used to examine the responsiveness of the PROMIS domains to
develop Minimum Clinically Important Differences (MCIDs) for this patient population.

**Randomization:** Not applicable

**Safety monitoring:** Not applicable
1. KEY ROLES

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

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

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

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

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

2.1 Background Information

Despite substantial improvements in care for limb trauma made over the last two decades, these injuries often result in significant long-term consequences for previously healthy young individuals with many remaining years of potentially productive life. Orthopaedic limb injuries result in nearly 700,000 hospitalizations each year, and account for nearly $20 billion in productivity losses alone. Orthopaedic trauma has gained increased attention recently as a result of its high impact among returning service members from the wars in Afghanistan and Iraq.

Clinical effectiveness evaluations are essential for identifying the optimal treatment for orthopaedic trauma patients, particularly those experiencing psychologic distress and pain following their injury who are at increased risk of poor long term outcomes. However, key barriers in the measurement of trauma outcomes have hampered research in this field. First, the multi-factorial nature of trauma outcomes requires the use of multiple measures, which can be costly to collect and burdensome to patients. Second, outcomes are time dependent and measures must be responsive to wide variation in outcomes trajectory. PROMIS item banks, developed under the NIH Roadmap initiative, can address these challenges through computer-adaptive tests or CATs. CATs offer short, precise measures, making measurement across multiple domains feasible. CATs can also extend the ceiling and floor of individual domains, potentially enhancing responsiveness. The publically available PROMIS item banks have the potential to form the basis for a standardized measurement strategy, which can facilitate the conduct of studies and the synthesis of research findings, significantly advancing the field of trauma outcomes research.

The PROMIS item banks and tools have not been fully tested among orthopaedic trauma patients, especially in the context of orthopaedic clinical trials. The proposed project will aim to address these problems by examining the relevance and measurement properties of PROMIS tools in this population and setting. The overall strategy will be to leverage the existing infrastructure of a large orthopaedic trauma clinical trials consortium, the Major Extremity Trauma Research Consortium (METRC).

2.2 Rationale

The proposed research will significantly advance orthopedic trauma research and practice, and will contribute to the application of patient centered outcomes research. The products of this project will include: 1) empirical evidence of the temporal stability, validity and responsiveness of PROMIS CATs and short forms in orthopaedic trauma populations; 2) a demonstration of the feasibility of the use of the PROMIS tools within the framework of a large clinical trials consortium; and 3) validation of the applicability of items in the current PROMIS item banks to this patient population, determined through differential item functioning analyses. We expect that these products, supported by PROMIS resources, will significantly advance the field of trauma outcomes research by facilitating the use of a common measurement strategy for future clinical trials and outcomes research in trauma populations.
2.3 Potential Risks and Benefits

2.3.1 Potential Risks

Any time information is collected for a study, there is a small risk of breach of confidentiality. However, this risk is not greater than the risk that already exists in clinical settings when handling medical data.

2.3.2 Potential Benefits

While there are no direct benefits to patients participating in the study, we expect that the outcomes of this study, supported by PROMIS resources, will significantly advance the field of trauma outcomes research by facilitating the use of a common measurement strategy for future clinical trials and outcomes research in trauma populations and potentially minimize respondent burden.

3. STUDY OBJECTIVES

The overall goal of this study is to examine the reliability, validity and responsiveness of the PROMIS tools for clinical research following orthopaedic trauma.

3.1 Primary Objective

Examine the measurement properties of existing PROMIS CATs and item banks in patients with orthopaedic trauma. We will incorporate ten (six core and four exploratory) PROMIS short form and CATs into the longitudinal data collection of four ongoing orthopaedic trauma clinical trials and administer an expanded data collection interview at the time of their last study follow up which will be used to:

1a: Evaluate reliability and construct validity of the PROMIS CATs
1b: Compare measurement precision of the six existing item banks when applied in an orthopaedic trauma population versus the general population.
1c: Identify items from existing PROMIS item banks that function differently in our population compared with the general population.

3.2 Secondary Objectives

Examine the responsiveness of existing PROMIS domains in patients with orthopaedic trauma. Specifically, we will:

2a: Examine the responsiveness of PROMIS domains against expected clinical recovery in this population.
2b: Examine the responsiveness of PROMIS domains against well-defined clinical inflection points in the recovery process, such as infections, non-unions, flap failures, and other complications.

2c: Examine the responsiveness of PROMIS domains against treatment effects observed for interventions being studied in these trials, which include a psychosocial intervention, a pharmacologic intervention, and a device. These trials are being evaluated using widely used traditional outcome measurement tools.

3. Study the integration of the PROMIS tools within the data collection infrastructure of METRC. Key feasibility components examined will be integration with our distributed electronic data capture system (REDCap), and use of the CAT technology across dozens of trauma centers and orthopaedic trauma clinics.

3a. Compare the rate of use of CAT-based assessment versus short-form data collection
3b: Compare the data completeness using existing METRC approaches, CAT and short form PROMIS instruments
3c: Compare respondent burden using existing METRC approaches, CAT and short form PROMIS instruments.

3.3 Exploratory Objectives

N/A

4. STUDY OVERVIEW

This is an add-on study to four existing METRC studies. Patients recruited into these studies all return to the treating facility 3 months following injury or definitive treatment. At this visit, patients will be offered the opportunity to participate in the STREAM study. If they choose to participate, they will be assigned a study identification number and co-enrollment will be noted.

Once written informed consent is obtained, study participants will complete a series of computer adaptive testing (CAT) questions covering all core and exploratory domains. Administration of these surveys will follow completion of all other follow-up activities related to the main METRC study in which they were originally enrolled. Identical surveys will be repeated at the 6 month study visit. At the final 12 month study visit, participants will complete the CAT survey for the six core domains, and will also complete a randomly assigned subset of items from the total item bank across these six core domains. At any visit, if the CAT cannot be administered, respondents will instead complete paper surveys of the short form for each domain.

5. STUDY POPULATION

5.1 Description of the Study Population

Approximately 1,000 adult participants will be enrolled from METRC core civilian trauma centers, military treatment facilities and METRC satellite centers over an 18-month period. Core
centers are large Level I trauma centers with large numbers of severe orthopaedic injuries and includes sites with a proven track record for successfully recruiting and retaining participants in prospective studies in orthopaedic trauma. Satellite centers are smaller civilian trauma centers that elect to participate in selected METRC studies, as study recruitment needs align with center interests. Participants will be recruited at the time of the 3-month study visit associated with the main METRC study they were originally enrolled in. Consenting procedures are described in detail in Sections 8 and 13 of this protocol.

5.1.1 Participant Inclusion/Exclusion Criteria

Any patient participating in the FIXIT, OUTLET, TAOS, Oxygen or Pain studies returning for a 3 month follow-up visit is eligible for participation in the proposed STREAM study. Respondents who are unable to give informed consent (or would require a proxy) at the time of the 3 month visit will be excluded.

5.1.2 Co-Enrollment Guidelines

Patients participating in this study are by design co-enrolled in a subset of other METRC studies. There are no restrictions on co-enrollment with these or any other METRC or non-METRC studies.

6. STUDY PROCEDURES

6.1 Screening and Enrollment

6.1.1 Screening

All participants in the FIXIT, OUTLET, TAOS, Oxygen or Pain studies are eligible for participation in the STREAM study. There is no formal screening process, although an enrollment form will be completed for each patient, assigning a study id and linking the patient to other METRC studies.

6.1.2 Consent and Enrollment

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

Once eligibility has been confirmed, the informed consent process will be completed by the Research Coordinator. Informed consent will be obtained at the time of the 3-month study visit for the original METRC study, and must be obtained from the participant. No LARs or proxy consent will be used in this study.
A version of all study materials will be provided in both English and Spanish. Participants unable to use the English-language METRC CAT application, will be able to use Spanish-language paper based short forms.

Recognizing that consent is an ongoing process, the study team will encourage the participants to ask additional questions that may arise during the course of their participation in the study.

6.2 Baseline Data Collection

Once consented into the study, participants will be assigned a study id by the PROMIS application. After completing the assessment associated with the main METRC study in which they were originally enrolled, participants will complete a brief 10-12 minute survey using the CAT on an iPad, a desktop, or other similar tablet device provided for this purpose. In the event the CAT version of the items cannot be administered, a paper version of the short form covering the same domains will be administered.

6.3 Participant Follow up and Data Collection

6.3.1 Follow-up Visit Schedule

Participants will participate in follow-up visits at 6 and 12 months, according to the schedule of the main METRC study in which they were previously enrolled. At the 6 month visit, participants will complete a brief 10-12 minute CAT survey on an iPad, desktop, or other tablet device provided for this purpose, as was done at baseline. At the time of the 12 month visit, participants will complete the CAT survey for the six core domains, and will also complete a 20-30 minute survey that includes a subset of items from the total item bank from these six core domains. In the event that a visit does not occur in person, the items can be completed on a paper form, by telephone, or a unique electronic link to the online survey platform identified only by study id can be sent to the participant.

Each visit will have a time window surrounding the ideal date for the visit during which the visit may be completed and the data included in the trial database. This interval is defined by the original study into which the participants were enrolled.

Because the parent METRC studies already collect a set of standard PRO instruments (the SMFA, BPI, PHQ9, and PCL), we will not need to collect those instruments as part of this project in addition to the PROMIS items.

6.3.2 Retention

Every effort will be made to retain participants in the study. The study participants will receive an honorarium in recognition of their time and effort: $10 will be given for completing the 3-month and 6-month visits and $30 will be given and the final, 12-month follow-up visit, for a
total of $50. This is in addition to the honoraria they will receive as participants in the original METRC study, and recognizes the additional time required to complete surveys.

6.3.3 Final Study Visit

Participants will complete the study at month 12.

6.3.6 Early Termination Visit

Should a participant terminate the study prematurely, if at all possible, the participant will complete the questionnaire using items from the total bank at the final visit.

6.4 Study Endpoints

6.4.1 Primary Endpoint

The primary endpoint for this study is the reliability and construct validity of the PROMIS CAT instruments.

6.4.2 Secondary Endpoints

The study will evaluate the following secondary endpoints:

- Responsiveness against clinical recovery, inflection points and effective interventions.
- Rate of use of CAT-based vs short form paper-based data collection
- Data completeness in CAT-based instruments vs short form paper-based data collection
- Respondent burden, as indicated by time to complete instrument, which will be recorded by the CAT, and manually recorded at start/stop time on the paper short forms.

6.4.3 Exploratory Endpoints

N/A

7. STUDY TREATMENTS

This is an observational study. As such, there are no study treatments.

8. ASSESSMENT OF SAFETY

Patients will be followed and their safety evaluated according to the original METRC protocol. No patient will be placed at increased risk as a result of participating in the STREAM study, and as such, no additional assessments of safety are required.

In the event a participant dies while being followed as part of this study, the event will be reported to the local IRB and MCC under the original METRC study there were enrolled in. At
the time of annual renewal, a list of all participant deaths will be reported to the Johns Hopkins
IRB and the local IRB.

8.1 Reporting Pregnancy

N/A

8.2 Premature Withdrawal of a Participant

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

9. MONITORING

9.1 Site Monitoring Plan

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

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

9.2 Safety Monitoring Plan

9.2.1 Safety Review Plan by the DSMB

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

The Medical Monitor for this study is:

Mark Swiontkowski, MD, FACS
Department of Orthopedic Surgery
2450 Riverside Ave., R200
Minneapolis, MN 55454
Telephone: (612) 273-7951
Fax: (612) 273-7959
E-mail: swion001@umn.edu
10. STATISTICAL CONSIDERATIONS

10.1 Sample Size Considerations

Assuming power = 0.80 and alpha = 0.05, we would need 309 in each group to detect an effect size of 0.2 (http://www.dssresearch.com/KnowledgeCenter/toolkitcalculators/samplesizecalculators.aspx) and 153 subjects to detect a significant correlation of 0.2 (http://www.stattools.net/SSizcorr_Tab.php). Based on the >1000 participants included in the construct validity analyses, we expect to have more than adequate power to detect meaningful differences based on those observed in the literature on functional outcomes for patients with major lower limb trauma. Similarly, we will be well-powered to conduct the responsiveness analyses. As an example, even assuming an overall infection rate of 10%, we would be 80% powered (at alpha=0.05) to detect an effect size of 0.3. This would be a worst-case scenario, as we expect all other comparisons to be based on more evenly distributed groups. The driver of sample size for this study will be the DIF analyses requiring collection of full item banks. Because prior studies have identified 200-300 as an adequate range for this type of analysis, we will based our sample size on the need to collect 250 full item banks sets (Edelen, Reeve, 2007). In order to reduce study burden, we will split the collection of full item banks across the entire study population.

10.2 Randomization

All eligible patients will be enrolled in the study. The application used to administer the PROMIS CATs will randomly allocate exploratory domains and item sets to patients.

10.3 Missing Data and Measures to Minimize Bias

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

1. Limit participant burden and inconvenience in data collection
2. Select high quality investigators
3. Provide pre-study training of investigators as well as on-study reinforcement
4. Reimburse investigators based on follow-ups completed not on per-patient basis.
5. Monitor and report missing data rates during the study
6. Emphasize the importance of full participation in the study during the consent process.
7. Collect information on the reasons for missing data.
8. Actively engage participants and educate them about the importance of participation
9. Hold regular Protocol Committee meetings to discuss strategies for follow-up
10. Set targets for acceptable rates of missing data and terminate sites not meeting targets.
While these efforts will help to minimize missing data, we recognize that missing data is inevitable. With this in mind, we will conduct sensitivity analyses to evaluate the robustness of the study results to missing data mechanism.

10.4 Planned Interim Analysis

N/A

10.5 Analysis Plan

**Aim 1:** We will evaluate whether PROMIS CAT scores demonstrate adequate reliability (test-retest reliability) and construct validity (convergent, discriminant, known group and criterion validity) in the orthopaedic trauma population. Using data from the full item banks administration at the 12 month visit, we will compare measure precision and the measurement equivalence (evaluated through differential item function analysis) of the PROMIS item banks in our clinical sample relative to the general U.S. PROMIS calibration sample.

**Construct Validity:** Confidence in the PROMIS CAT scores for our target population will increase if evidence of construct validity accrues from a variety of different tests, including concurrent convergent, discriminant, known group, and criterion validity tests. The measures used for these analyses are summarized in Table 3.

For **convergent validity**, we will examine the cross-sectional relationship between PROMIS CATs and “legacy” measures for the same domain. Specifically, we expect to find moderate ($r > 0.40$-$0.6$) positive associations of PROMIS tools with these validation measures, as measures of the same construct should demonstrate moderate-to-strong associations with each other. For example, Miller et al. (2008) has observed correlation of between 0.57-0.71 for measures of depression and mental health, and vitality and fatigue.

For **discriminant validity**, we will examine the cross-sectional relationship between PROMIS CATs with measures of other PROMIS domains, specifically selected to have weaker correlation with the PROMIS domain under study than legacy measures of the same domain. For example, we will expect weak to moderate correlation between PROMIS physical function with depression and anxiety. Miller et al. (2008) has observed correlation of -0.37 for depression and physical function measures.

For **known-group validity**, groups will be created based on injury severity, educational attainment, social support, and self-efficacy (Bosse et al, 2002). We expect to see worse physical function for participants with Gustilo III fractures than patients with closed and Gustilo I, and II fractures, because of impairments caused by loss of muscle compartments and nerve function. We also expect worse social participation scores for those who did not graduate high school compared with those who did graduate or have some college education. We will perform 2-sample t-tests for these hypothesized group differences.

For **criterion validity**, we will examine concurrent association between PROMIS CATs with different measures of clinical condition. We will examine the association of PROMIS CAT scores with level of recovery: 1) weight bearing status; 2) fracture union.
status; 3) soft tissue healing status; and 4) return to usual major activity. We expect better outcomes for those who have achieved these well established recovery thresholds.

Table 1. Validation, Grouping, Comparison or External Measures

<table>
<thead>
<tr>
<th>Construct Validity</th>
<th>Validation, Grouping, Comparison or External Measures</th>
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</thead>
<tbody>
<tr>
<td>Analysis</td>
<td></td>
</tr>
<tr>
<td>Convergent</td>
<td>Established conventional measure of domain</td>
</tr>
<tr>
<td>Discriminant</td>
<td>Other PROMIS domains expected to have modest or weak correlation</td>
</tr>
<tr>
<td>Known Group</td>
<td>Open Fracture Injury severity: Gustilo Classification</td>
</tr>
<tr>
<td></td>
<td>Open Fracture Injury severity: OTA Open Fracture Classification</td>
</tr>
<tr>
<td></td>
<td>Education: &lt; HS; HS or more</td>
</tr>
<tr>
<td></td>
<td>Socioeconomic Status: Federal poverty guidelines</td>
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<tr>
<td></td>
<td>Social Support: BRFSS Single Item Measure of Social Support</td>
</tr>
<tr>
<td></td>
<td>Self Efficacy for Return to Usual Major Activity</td>
</tr>
<tr>
<td>Criterion</td>
<td>Clinical Recovery: Weight Bearing Status</td>
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<tr>
<td></td>
<td>Clinical Recovery: Fracture Union Status</td>
</tr>
<tr>
<td></td>
<td>Clinical Recovery: Soft Tissue Healing Status</td>
</tr>
<tr>
<td></td>
<td>Community Reintegration: Return to Usual Major Activity</td>
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</table>

**Measure precision:** Data from the full bank administrations will be used to generate total information and standard error functions to assess their measure precision. These will be compared to the information and standard errors functions from the PROMIS general population calibration sample. These graphs will allow us to determine whether the item banks offer the same level of precision for both samples.

**DIF identification.** An item demonstrates differential item function if the probabilities of responding to the response categories in the item differ by the group of interest for individuals with the same level of underlying trait (Reeve et al., 2007). It is important to establish measurement equivalence of the PROMIS domain items for our trauma population compared with general population. In addition, since different items can be administered to different individuals in CATs, it is particularly important to be able to identify items with DIF to minimize their influence on CAT estimates. For these analyses, we will use the graded response model (Samejima 1997), implemented with the computer program **Multilog** to estimate discrimination and location parameters for each item. We selected the GRM because of its flexibility in parameter estimation and because it is the IRT model used for item calibration in PROMIS (Reeve et al., 2007).

Using data from the full bank administrations, we will employ the DIF methods used by PROMIS (Reeve et al., 2007) to identify uniform (location) and non-uniform (discrimination) DIF. Identifying an anchor set is a key part of DIF identification. We will use IRTLRDIF program (Thissen, 2001) to identify, through a series of iterative analyses, a set of anchor items that are free of DIF in both groups and that can serve to link the two groups on a common scale. Using these anchor items, we will first use IRT likelihood ratio (IRT-LR) tests which compares nested IRT models, with one model fully constraining IRT parameters to be equivalent in the two groups under comparison and the other allowing the item parameters to be freely estimated in the
groups (i.e., the discrimination \((a)\) parameter, the location \((b)\) parameters, both \(a\) and \(b\) parameters). We will use, in combination with IRT-LR, Raju’s signed and unsigned area tests and the DFIT framework to obtain magnitude measures of DIF. The second method involves the use of ordinal logistic regression (OLR) models, in which a series of 3 models (Model 1: trait, group, trait*group interaction; Model 2: trait, group; Model 3: trait) predicting the probability of item response are compared. Likelihood ratio comparisons of Models 1 and 2 help identify non-uniform DIF. Similar comparisons of Models 2 and 3 identify uniform DIF. Relative change to beta estimates between Models 2 and 3 will be examined, with 10% change in beta used as a criterion for uniform DIF. Finally, we will use a hybrid method that combines the strengths of IRT-LR and OLR, using IRT person theta estimates iteratively with the ordinal logistic models. To account for false positive or negative DIF results, group specific item parameters are estimated for items showing DIF in the first run (DIF-free items serve as anchor items). DIF identification is repeated with these updated IRT parameters. New IRT estimates based on this second DIF analysis will be used to feed another round of DIF identification. This cycle of DIF identification and IRT estimation is repeated until the same DIF items are identified in successive runs.

**Aim 2:**

*Measuring responsiveness against expected clinical recovery:* Trauma outcomes are generally experienced as part of a natural recovery process. This recovery process tends to exert its largest effects on physical function and social participation, depending on baseline functioning and the type and severity of the trauma. We will assess measure responsiveness against this recovery trajectory in the PROMIS domains that we hypothesize would improve over the course of the 9-month data collection period (e.g., physical function, social participation). For each domain, we will also ask each respondent to report on health transitions (i.e., changes in the domain during the period from the baseline to 6 months), using an approach similar to that of Juniper et al. (1994). We will categorize our sample into: 1) improved, 2) unchanged, and 3) worsened groups based on these respondent reports. We will then conduct an ANOVA to test for a graded group differences in change scores across these three groups. In addition, we will examine the association of change scores for the domain, controlling for or stratified by baseline score, with: 1) return to work after 6 months; and 2) recovery to baseline functioning (Dikmen et al., 2003). Within any baseline domain score group, we will expect that a larger positive score change will be associated with stronger recovery to baseline function.

*Measuring responsiveness against clinical inflection points:* We will examine the responsiveness of PROMIS domains against well defined clinical inflection points in the recovery process, such as infections, non-unions, flap failures, and other complications, all of which have been documented to result in expected changes in patient reported outcome. We hypothesize that there will be statistically significant differences in change scores between those individuals who experience clinical recovery setbacks and those who do not. As above, we will conduct an ANOVA to test for group differences in change scores across these clinical groups.

*Measuring responsiveness against effective interventions:* We will examine the responsiveness of PROMIS domains against the interventions being studied in these trials, which include a psychosocial intervention, a pharmacologic intervention, and a device. These trials are being evaluated using widely used outcome measurement tools. As above, we will conduct an ANOVA to test for group differences in scores across these treatment groups.
Aim 3:

Descriptive statistics will be reported, allowing comparison of the rates of use of the CAT vs the short forms, data completeness, and participant burden.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Data Quality Assurance

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

11.2 Training and Certification of Centers

All participating centers together with their respective study personnel will undergo certification that included training, local site IRB, and a knowledge assessment on the study design and procedures. This training will include participation in a Web Ex training for research coordinators, and will include information on how to administer the surveys using the CAT technology and manage data transfer from the local device to REDCap.

12. ETHICS/PROTECTION OF HUMAN SUBJECTS

12.1 IRB/Ethics Committee

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

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

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

12.3 Participant Confidentiality

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

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

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

12.4 Study Discontinuation

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

13. DATA HANDLING AND RECORD KEEPING

13.1 Data Management Responsibilities

Once participants are enrolled, site Research Coordinators will complete an enrollment case report form, which will contain study ID and linkers to other METRC studies. The STREAM study ID will also be recorded in a central administrative database tracking patient specific study ids for all METRC studies in which individual patients are enrolled. This information will be entered into a central and secured web-based data management system being implemented for all Consortium studies, known as REDCap. This data management system has incorporated state-of-the-art features for electronic data collection and is configured in accordance with best practices for information technology and research data management.
All research data, in hard copy or electronic form, will be stored and managed in a secure manner following applicable federal regulations and ICH guidelines and according to institutional policies and practices. Hard copy documents containing subject data, patient identifiers and contact information will be stored in secure, locked containers (file cabinets, drawers, etc.) in accordance with standard document management practices.

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

13.2 Data Capture Methods

Data will be collected by administering all survey instruments using a tablet device, or if not available, a paper short form. Data collected on paper forms will be identified by study ID and uploaded to REDCap by the research coordinator or another MCC-certified staff member. Data recorded using a tablet device will not contain any patient identifiers. Data will be securely transmitted to the METRC database server (which also hosts the METRC REDCap application) and linked to other data using only the patient's study ID. In the event a connection to the METRC database server is not available at the time of data collection, the data collected will be remain encrypted until such time the tablet can establish a connection to the server. Once transferred to the MCC, data collected on the device will no longer be available from that device.

13.3 Types of Data

Data will include patient responses to survey items. The study will team will have the ability to match these data to data collected as part of the original METRC study, including medical and surgical histories, laboratory reports, radiology reports, clinical evaluations, performance assessments, adverse events and patient interviews.

13.4 Source Documents and Access to Source Data/Documents

There are no source documents associated with the proposed data capture methodology. All data are patient-reported outcomes.

13.5 Study Records Retention

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

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

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

15. SCIENTIFIC REFERENCES

References
## APPENDICES

### APPENDIX A: STUDY CONTACT ROSTER

<table>
<thead>
<tr>
<th>Principal Investigator (Protocol Chair)</th>
<th>METRC Coordinating Center</th>
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<tbody>
<tr>
<td>Renan Castillo, PhD</td>
<td><strong>Director of Protocol Development</strong></td>
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<tr>
<td>Johns Hopkins Bloomberg School of Public Health</td>
<td>Katherine Frey, MPH, RN/ Lisa Reider, MHS</td>
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<tr>
<td>Dept. Health Policy and Management</td>
<td>Johns Hopkins Bloomberg School of Public Health</td>
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<tr>
<td>415 N. Washington Room 301</td>
<td>Dept. of Health Policy and Management</td>
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<tr>
<td>Baltimore MD, 21231</td>
<td>415 N. Washington Room 353/351</td>
<td></td>
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<tr>
<td>Phone: 410- 614-4024</td>
<td>Baltimore MD, 21231</td>
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<tr>
<td>Email: <a href="mailto:rcastill@jhsph.edu">rcastill@jhsph.edu</a></td>
<td>Phone: 410-502-9109/410-502-3962</td>
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<tr>
<td></td>
<td>Email: <a href="mailto:kfrey@jhsph.edu">kfrey@jhsph.edu</a>/lsemanic@jhsph.edu</td>
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<tr>
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<th>METRC Coordinating Center</th>
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<tr>
<td></td>
<td><strong>Director of Data Management</strong></td>
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<tr>
<td></td>
<td>Anthony Carlini, MS</td>
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<td></td>
<td>Baltimore MD, 21231</td>
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<tr>
<td></td>
<td>Phone: 410-502-8455</td>
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<tr>
<td></td>
<td>Email: <a href="mailto:acarlini@jhsph.edu">acarlini@jhsph.edu</a></td>
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</tbody>
</table>

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APPENDIX B: PROTOCOL COMMITTEE

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Carolinas Medical Center  Johns Hopkins School of Medicine

Albert Wu, MD, MPH  Kitty Chan, PhD  
Johns Hopkins Bloomberg School of Public Health  Johns Hopkins Bloomberg School of Public Health

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Johns Hopkins Bloomberg School of Public  San Francisco General Hospital

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University of Utah  University of Maryland, R. Adams Cowley Shock Trauma Center

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Lisa Reider, MHS  Katherine Frey, MPH, RN  
Johns Hopkins Bloomberg School of Public Health  Johns Hopkins Bloomberg School of Public Health

Anthony Carlini  
Johns Hopkins Bloomberg School of Public Health
### APPENDIX C: DATA COLLECTION SCHEDULE

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Baseline (3 mos)</th>
<th>6mo</th>
<th>12mo</th>
<th>12 mos</th>
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<tbody>
<tr>
<td><strong>Core PROMIS Domains</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ability to participate in social roles and activities</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Depression</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Anxiety</td>
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<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Psychosocial impact- positive</td>
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<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pain interference</td>
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<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Physical function</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td><strong>Exploratory PROMIS Domains</strong></td>
<td></td>
<td></td>
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<tr>
<td>Satisfaction with participation in social roles</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Applied cognition</td>
<td></td>
<td></td>
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<tr>
<td>Emotional support</td>
<td>X</td>
<td>X</td>
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</table>

*Each participant will complete a randomly assigned subset of the full item bank across domains
APPENDIX D: CONSENT TEMPLATE

JOHNS HOPKINS BLOOMBERG SCHOOL OF PUBLIC HEALTH

INFORMED CONSENT DOCUMENT

Patient Consent Form

Study Title: Streamlining Trauma Research Evaluation with Advanced Measurement: STREAM Study
Principal Investigator: Renan Castillo, PhD
IRB No.: TBD
PI Version Date: 3/9/15

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

1. WHAT IS THE PURPOSE OF THIS RESEARCH STUDY?
   The purpose of this study is to test questions related to important outcomes in patients with orthopaedic injuries. These questionnaires were developed as part of the National Institute of Health’s Patient Reported Outcomes Measurement Information System (PROMIS). They will include questions about how you are feeling and about anxiety, stress and pain that you may be experiencing. There will also be questions about your social interaction with others, the emotional support you receive, your physical function, and your sleep habits. These questions are shorter than most surveys currently being used to assess patient outcomes, and they can be taken on a paper form or on a computer or tablet device. These questions have not been tested among people with serious orthopaedic injuries. We will compare your answers to these questions to your answers on similar surveys completed for the METRC study you are participating in. We will also be looking at how long it takes for patients to respond to these questions.

2. WHY AM I BEING ASKED TO PARTICIPATE?
   You are being asked to participate in this study because you are currently a participant in another METRC (Major Extremity Trauma Research Consortium) study. Only participants in METRC studies are eligible to take part in the STREAM study. In total, about 1,000 patients will participate in this study.

3. HOW LONG WILL THE STUDY LAST?
   If you agree to participate in the STREAM study, you will be in the study until you complete the 12 month follow up visit for the METRC study you are currently enrolled in. You may
be asked to complete an extra visit as a result of your participation in this study, if your METRC study visit does not take place in person. If you prefer, you could answer these questions by telephone, by mail, or electronically.

4. HOW DOES THE STUDY WORK?
   If you agree to participate, you will be asked to complete a questionnaire either using a computer or tablet like an ipad or on a paper form either in person or by telephone. This questionnaire should take you 10-12 minutes to complete. You will be asked to complete this questionnaire during the 3 and 6 month METRC study follow-up visits. At the final 12 month METRC study follow-up visit you will also be asked to complete an additional 20-30 minute questionnaire, in person, or by telephone, mail, or electronically if the visit does not take place in person.

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

6. WHAT ARE THE POTENTIAL BENEFITS?
   You will not benefit directly from your participation in this study. However, your participation in the study could help us design better questionnaires for understanding how people recover after experiencing injuries like yours. This information could be very helpful to other people who have this same injury in the future.

7. DO I GET ANY PAYMENT FOR BEING IN THE STUDY?
   You will receive $10 for completing the 3 and 6 month visits, and $30 for completing the 12 month visit, for a total of $50. This is over and above any payments you may receive for your participation in the original METRC studies. These payments are in appreciation of your time and effort.

8. ARE THERE ANY COSTS INVOLVED IN BEING IN THE STUDY?
   There is no cost to you to participate in this study.

9. WILL MY INFORMATION BE KEPT PRIVATE?
   By signing this form, you give permission for your health information to be used and shared for the purposes of this study. All research projects carry some risk that information about you may become known to people outside of the study. <<Insert Clinical Center Name>> has rules to protect information about you. Federal and state laws also protect your privacy. This part of the consent form tells you what information about you may be collected in this study and who might see or use it. We will keep your records in a secure place. Only clinical center staff or people authorized to audit the study will have access to the study forms. We
try to make sure that everyone who needs to see your information keeps it confidential – but we cannot guarantee this.

The people working on the study at this clinic will collect information about you. This includes things learned from the answers you give to the questions described here and other information including your name, and contact information (such as address). Your name and other identifying information will be kept private.

We cannot do this study without your permission to use and give out your information. You do not have to give us this permission. If you do not give us this permission, then you may not join this study. Generally, only people on the research team will know that you are in the research study will see your information. A unique number and special code will be used in place of your name for data entry. The number and code cannot be linked to your name except at the clinical center where you complete your visits. Data collected from your study visits will be labeled with the unique number and special code only. Study data will be sent to the Data Coordinating Center at Johns Hopkins University, in Baltimore, Maryland.

You may cancel your decision to share your health information at any time by contacting the study coordinator or director using the information included in item #14 below. After the study personnel receive your cancellation, no new information will be collected about you. If you cancel, the research team will still be allowed to use the information that was collected prior to your cancellation.

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

The National Institutes of Health is providing funding to sponsor this study. Federal representatives and your local IRB may have access to research records in their role to protect human subjects engaged in research.

11. WHAT ARE MY ALTERNATIVES TO PARTICIPATION?
Your alternative is to not take part. If you choose not to take part, your healthcare will not be affected.

12. WHAT HAPPENS IF I LEAVE THE STUDY EARLY?
Your participation in this study is completely voluntary. You have the right to withdraw from the research study at any time without penalty. Your decision will not affect the medical care you receive. If you decide to stop participating, you should notify the study doctor or the research coordinator at your center.
Your participation in this research study could be ended without your consent. Possible reasons could include our decision to end the study early or other reasons.

13. WHAT HAPPENS IF I AM INJURED OR BECOME ILL BECAUSE I TOOK PART IN THIS STUDY?
It is very unlikely that you will become ill or be injured because of your participation in this study. If this does happen, you will receive emergency medical care if needed and you will receive assistance in getting other medical care as needed. You or your insurance carrier will be billed for the cost of care, just as you would be billed for any other medical care. If you have any costs that are not covered by insurance, they are your responsibility.

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

14. WHO DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?
- **<<insert name>>**, the study coordinator at your hospital has discussed this information with you and offered to answer any questions you may have. If you have further questions or get sick or injured as a result of being in this study, you can contact **<<insert him/her>>** at **<<telephone number>>**. You may also call the Director of the Study at your hospital, **<<insert name>>**, at **<<telephone number>>**.
- If you have further questions about your rights as a study participant you can call or contact the Johns Hopkins Bloomberg School of Public Health IRB Office. The Johns Hopkins Bloomberg School of Public Health is serving as the overall coordinating center for this study that is being conducted in hospitals around the country. Contact the Johns Hopkins IRB if you feel you have not been treated fairly or if you have other concerns. The IRB contact information is:
  Address:    Johns Hopkins Bloomberg School of Public Health
              615 N. Wolfe Street, Suite E1100
              Baltimore, MD  21205
  Telephone:  410-955-3193
  Toll Free:  1-888-262-3242
  Fax:        410-502-0584
  E-mail:    irboffice@jhsph.edu
What does your signature (or thumbprint/mark) on this consent form mean?
Your signature (or thumbprint/mark) on this form means:
- You have been informed about this study’s purpose, procedures, possible benefits and risks.
- You have been given the chance to ask questions before you sign.
- You have voluntarily agreed to be in this study.

Print name of Adult Participant  Signature of Adult Participant  Date

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

Print name of Person Obtaining Consent  Signature of Person Obtaining Consent  Date

Give one copy to the participant and keep one copy in study records