University of Maryland, Shock Trauma Center
Department of Orthopaedics

Impact of Surgery on Pain in Lateral Compression Type Pelvic Fractures: A Prospective Trial (Pelvis RCT)

NCT02605766

University of Maryland IRB Number: HP-00060038

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Safety Monitor: Andrew Pollak, MD

Version 4

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TABLE OF CONTENTS

PROTOCOL SUMMARY

Title	Impact of surgery on pain in lateral compression type pelvic fractures: a prospective trial
Short Title	Pelvis RCT
Type of Study	Prospective randomized control trial OR observational outcomes study
Primary Objective	To determine if surgical stabilization of lateral compression type pelvic fractures decreases patient reported pain at 2 weeks post injury compared to non-operative management.
Secondary Objective	To explore associations between treatment and: 1. Patient reported pain up to 1 year post injury 2. Hospital length of stay 3. Time to first mobilization (bed to chair) 4. Narcotic use up to 1 year post injury 5. Work productivity & activity impairment up to 1 year post injury 6. Health related quality of life up to 1 year post injury 7. Pelvic specific functional outcome up to 1 year post injury 8. General function up to 1 year post injury
Sample Size	We will recruit a sample size of 130 patients (65 per arm) with a minimum of 2 week follow-up for the primary outcome
Diagnosis and Main Inclusion Criteria	Lateral compression type pelvic fracture amendable to both operative or non-operative treatment per surgeon opinion in patients between the ages of 18 and 80 years of age, inclusive.
Length of Follow-up	1 year

Study duration: We will recruit for a year and a half. Patients will be followed for 1 year. We estimate 4 years total.

Primary outcome measure: *Pain* as measured by using the arithmetic mean of the four pain severity items on the patient-reported Brief Pain Inventory assessment (BPI) 2-weeks following the patient's injury.

Secondary outcome measures: *Length of stay* will be determined by recording the admission date versus discharge date for the patient's index hospitalization. *Time to first mobilization (bed to chair)* will be determined using the physical therapy notes during the patient's index hospitalization and is defined as days post-injury and days post-operative treatment (if applicable) to time of first mobilization (bed to chair). *Narcotic use* will be determined by cross-referencing the patient's medical record during the index hospitalization and follow-up clinic appointments with patient-reported usage. *Work productivity and impairment* will be determined using the modified WPAI:SHP questionnaire. *Health related quality of life* will be measured using the VR-12 questionnaire. *Pelvic function* will be measured using the Majeed Pelvic Score.

Statistical analysis: We are interested in estimating the causal effect of operative treatment versus non-operative treatment in lateral compression type pelvic fracture patients. For all our

analyses, we will report estimates of the causal effects, standard errors, and confidence intervals. We will also report the results of tests of null hypothesis of no causal effect.

KEY ROLES

Safety Monitor- Dr. Andrew Pollak will be responsible for overseeing patient safety for the study. Dr. Pollak will review the enrollment numbers and medical compliance annually for the duration of the study.

Coordinating Center Principle & Sub-Investigators- Dr. Robert O'Toole (PI) and the sub-investigators will be responsible for developing a detailed study protocol, providing oversight on study progress and act to correct deficiencies in the conduct of the study. The PI and sub-investigators will also draft the main publications related to the study, and assist with patient consent.

Site Principle & Sub-Investigators- The site PI and sub-investigators will be responsible for oversight on local study progress. The site PI and sub-investigators will also contribute to the main publications related to the study, and assist with patient consent.

Coordinating Center Research Coordinator- Andrea Howe, research specialist, is 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 the research team members and site research coordinators, providing daily oversight and management of study implementation, performing data quality control and analysis of study results. The coordinating center research coordinator will also conduct monthly reports for each site.

Site Research Coordinator- The site research coordinator is responsible for communicating any problems or concerns with the coordinating center, maintaining all local study documentation, developing and maintaining the site IRB application and consent, and circulating any changes to study documents including protocols, case report forms, and IRB materials to the site research team members.

Research Team Members- The research team members are responsible for the conduct of the clinical study including patient enrollment, performing study procedures, data collection and conducting study follow-up visits.

BACKGROUND INFORMATION

Lateral compression type pelvic ring injuries remain the most common type of pelvic fractures encountered. There is a substantial amount of controversy surrounding the treatment of these injuries and there is evidence that both operative and non-operative treatment can be successful. The crux of the problem is determining which of these patients would benefit from early surgical stabilization and which will heal uneventfully without surgery. Many authors site patient pain

and inability to mobilize as indications for surgery, although there is conflicting evidence supporting this claim. The presence of chronic pain in the trauma population is a growing area of interest, and there is a push towards controlling pain more effectively in the acute setting. It remains to be proven that surgical intervention is more effective at decreasing acute and longer term pain.

RATIONALE

There is evidence in the literature to support both operative and non-operative treatment of patients with LC1 or LC2 pelvic fractures. There is conflicting evidence that surgical stabilization decreases acute pain and narcotic requirements, although patients are often counseled to that effect. We propose to prospectively randomize patients with lateral compression type pelvic fractures to non-operative versus operative treatment and track which group has less pain, less need for narcotic pain medications, and who mobilizes with physical therapy faster.

POTENTIAL RISKS

If the patient is randomized to operative treatment, he/she will be exposed to all of the risks associated with surgery under a general anesthetic including but not limited to: prolonged intubation, heart attack, stroke and death. These risks are extremely rare and will be explained to the patient and/or family by the anesthesia team, and a separate anesthesia consent will be obtained. The risks of the surgical procedure are rare but include: infection, wound break down, failure of hardware, and neurologic injury. A separate surgical consent will be provided to go into more detail of the risks of the procedure.

The risk of non-operative treatment is displacement of fracture with possible need for surgical intervention or prolonged protected weight-bearing. This is unlikely but will be monitored closely, as per our standard of care.

While the intake questionnaire and information gathered is of a sensitive nature (income, narcotic use, pain and psychiatric history) and it might cause the patient some discomfort to answer truthfully, all information will be kept confidential and no identifiers will be used in publication.

While every attempt will be made to keep all information confidential and the master link between the patient study number and personal identifiers will be destroyed at the completion of the study, there remains a risk of the potential for the loss/breach of confidentiality. This risk will be minimized by storing all paper questionnaires in a secure, locked location and all electronic data will be password protected.

There may be risks in this study which are not yet known.

POTENTIAL BENEFITS

While there are no direct benefits to patients participating in the study (except for those that may accrue from closer clinical observation as a study patient), participation may help determine the best treatment for lateral compression type pelvic fractures in the future.

PRIMARY OBJECTIVE

To compare 2-week post-injury assessments of patient reported pain of participants undergoing operative versus non-operative treatment following a lateral compression type pelvic fracture. We hypothesize that there will be a decrease in the Visual Analog Scale (VAS) pain scores in the operative group as compared to the non-operative group both during their hospital stay and in the short-term outpatient follow up.

SECONDARY OBJECTIVES

To compare assessments of narcotic use up to 1 year post injury of participants undergoing operative versus non-operative treatment following a lateral compression type pelvic fracture. We hypothesize that there will be a decrease in the narcotic requirements in the operative group as compared to the non-operative group throughout the 1 year follow up.

To compare assessments of time to first mobilization (bed to chair) with physical therapy of participants undergoing operative versus non-operative treatment following a lateral compression type pelvic fracture. We hypothesize that the operative group will mobilize out of bed to chair with physical therapy faster than the non-operative group.

EXPLORATORY OBJECTIVES

To explore associations between treatment and:

1. Hospital length of stay (index hospitalization)
2. Work productivity and activity impairment up to 1 year post injury
3. Health related quality of life up to 1 year post injury
4. Pelvic specific functional outcome up to 1 year post injury.

DESCRIPTION OF THE STUDY DESIGN

The Pelvis RCT study is a prospective randomized treatment trial to evaluate outcomes among operative versus non-operative lateral compression type fractures. If the patient does not agree to randomization, the patient will be asked to participate in the observational arm of the study. A schematic representation of participant enrollment can be found in the figure below.
A total of 130 patients will be enrolled (65 per arm). University of Maryland, Shock Trauma Center will act as the coordinating center for this study and all patient will be recruited from

University of Maryland, Shock Trauma Center and Indiana University Health Methodist Hospital.

Patients and/or the patient's legally authorized representative (LAR) will be approached for informed consent as soon as is feasible following determination of eligibility.

During the index hospitalization, participants will be asked to provide basic demographic information, health status and function prior to injury. Study injury characteristics will be obtained from the surgeon and the participant's medical record.

Participants will be prospectively followed at 2 weeks, 6 weeks, 3 months and 1 year post-injury. All follow-ups will occur in person at the hospital clinic follow-ups or over the phone and will consist of both a clinical examination (when applicable) and interview.

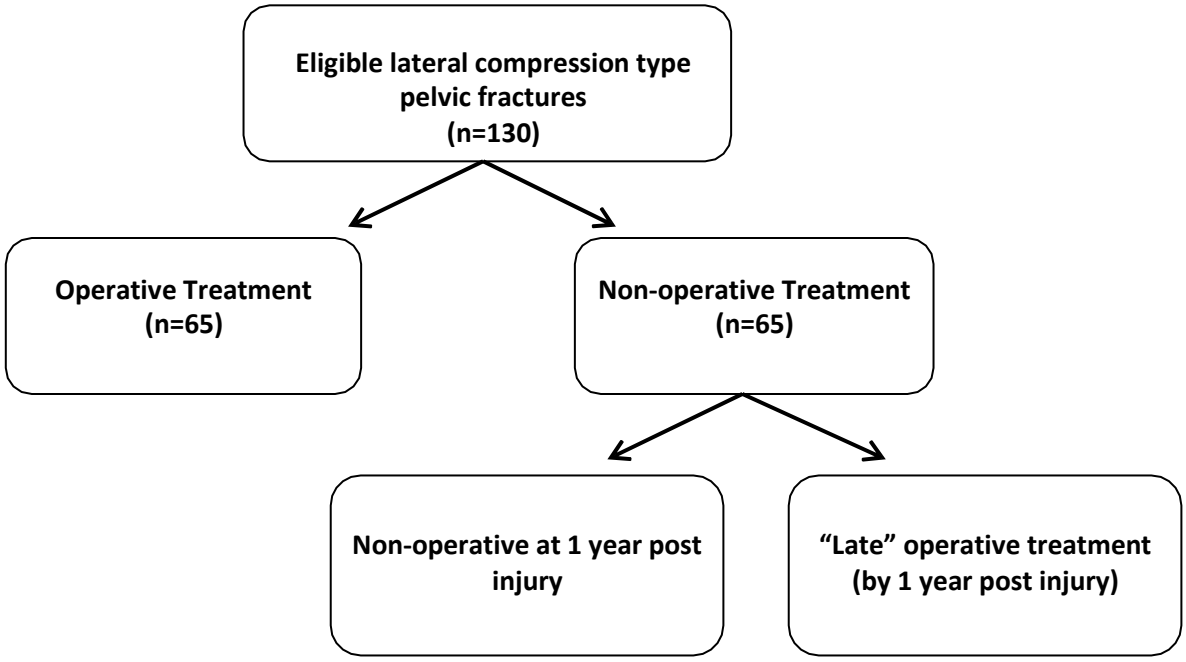

Figure: Participant Enrollment

PRIMARY ENDPOINT

The primary endpoint is *patient reported pain severity* as measured by the Brief Pain Inventory assessment (BPI). The BPI is a 15-item questionnaire that assesses the severity of pain, the impact of pain on daily function, the location of pain, pain medications and the amount of pain relief. There is no scoring algorithm but the arithmetic mean of the four severity items can be used as a measure of pain severity and the arithmetic mean of the seven interference items can be used as a measure of pain interference. This assessment has been chosen because it is a short, reliable, patient reported assessment of pain that has been specifically designed for and validated in patients with pain from acute conditions such as postoperative pain.

SECONDARY ENDPOINTS

The secondary endpoints include:

1. *Length of stay.* This will be found in the patient's medical record using the admission date and time versus the discharge date and time during his/her index hospitalization.
2. *Time to first mobilization (bed to chair)*. This will be found in the patient's medical record during his/her index hospitalization. Data will be found in the physical therapy notes and will be recorded as days post-injury and days post-operative treatment if applicable.
3. *Patient reported narcotic use*. This is will recorded by cross-referencing the patient's medical record and patient-reported questionnaire about pain medication use. The total narcotic use will be converted to the morphine equivalent for statistical analysis.
4. *Patient reported work productivity and activity impairment*. This will be measured using the modified Work Productivity and Activity Impairment (WPAI: SHP) assessment. The WPAI: SHP is a 6-item questionnaire that yields four types of scores: 1 – Absenteeism (work time missed); 2 – Presenteeism (impairment at work / reduced on-the-job effectiveness); 3 – Work productivity loss (overall work impairment / absenteeism plus presenteeism); and 4 – Activity impairment. WPAI outcomes are expressed as impairment percentages with higher numbers indicating greater impairment and less productivity, i.e., worse outcomes, as follows:

   Questions:

   a. currently employed
   b. hours missed due to pelvic injury
   c. hours missed due to other reasons
   d. hours actually worked
   e. degree pelvic injury affected productivity while working
   f. degree pelvic injury affected regular activities

   Scores:

   1. Percent work time missed due to pelvic injury:
      $[b \div (b + d)] \times 100$
   2. Percent impairment while working due to pelvic injury:
      $(e \div 10) \times 100$
   3. Percent overall work impairment due to pelvic injury:
      $(b \div (b + d) + [1 + (b \div (b + d)) \times (e \div 10)]) \times 100$
   4. Percent activity impairment due to pelvic injury:
      $(f \div 10) \times 100$
5. *Patient reported health related quality of life*. This will be measured using the VR-12…. Physical and Mental Health Composite Scores (PCS & MCS) are computed using the scores of the twelve questions and range from 0 to 100, where a zero indicated the lowest level of health measured by the scales and 100 indicates the highest level of health. Both Physical and Mental Health Composite Scales combine the 12 items in such a way that they compare to the national norm with a mean score of 50.0 and a standard deviation of 10.0.
6. *Patient reported pelvic function*. This will be measured using the Majeed Pelvic Score. The Majeed Pelvic Score uses five criteria chosen for functional assessment after major pelvic fractures: pain, standing, sitting, sexual intercourse and performance at work. Each

of these clinical parameters is scored, the total being a maximum of 100 points for patients who were working before the injury and 80 points for those who were not. The five sections of the assessment are scored as shown in Table I and discussed below. **Pain**. Pain is an important sequel of major pelvic injury, and is given a score of 30 points, allocated according to the six grades listed in Table I. **Standing**. Weight-bearing in the erect position is given 36 points, in three main categories (aids, gait and walking ability), each of which has six grades. **Sitting**. Sitting is an important function in relation to the pelvis, but less so than gait or walking ability. A total score of 10 points is given in four grades. **Sexual intercourse**. For both men and women, four points are allocated for comfort during sexual intercourse. This does not take account of neurological or psychological impotence and is recorded in four grades. If, for any reason, sexual intercourse has not been attempted, a score of four points is given. **Work**. Work performance is allocated 20 points in five grades, ranging from no regular work to return to the same job as before injury with no loss of performance. A patient who was not working at the time of his injury is not scored; his overall assessment is then out of 80 points.

Table I. System for functional assessment after pelvic fractures

Pain – 30 points	
Intense, continuous at rest	0–5
Intense with activity	10
Tolerable, but limits activity	15
With moderate activity, abolished by rest	20
Mild, intermittent, normal activity	25
Slight, occasional or no pain	30
Work – 20 points	
No regular work	0–4
Light work	8
Change of job	12
Same job, reduced performance	16
Same job, same performance	20
Sitting – 10 points	
Painful	0–4
Painful if prolonged or awkward	6
Uncomfortable	8
Free	10
Sexual intercourse – 4 points	
Painful	0–1
Painful if prolonged or awkward	2
Uncomfortable	3
Free	4
Standing – 36 points	
A Walking aids (12)	
Bedridden or almost	0–2
Wheelchair	4
Two crutches	6
Two sticks	8
One stick	10
No sticks	12
B Gait unaided (12)	
Cannot walk or almost	0–2
Shuffling small steps	4
Gross limp	6
Moderate limp	8
Slight limp	10
Normal	12
C Walking distance (12)	
Bedridden or few metres	0–2
Very limited time and distance	4
Limited with sticks, difficult without prolonged standing possible	6
One hour with a stick limited without	8
One hour without sticks slight pain or limp	10
Normal for age and general condition	12

The accumulative grading system is shown in Table II. This gives a breakdown into excellent, good, fair and poor for both working and non-working patients.

Table II. Clinical grade based on a score out of 100 points for working and 80 points for non-working patients (see text)

Working before injury	Not working before injury	Grade
>85	>70	Excellent
70 to 84	55 to 69	Good
55 to 69	45 to 54	Fair
<55	<45	Poor

STUDY POPULATION

The study population will be patients aged 18-80 with a lateral compression type pelvic fracture that go on to receive operative or non-operative treatment of the injury.

Inclusion Criteria:

1. Patients that have one of the following pelvic fractures (includes bilateral sacral fractures): lateral compression type 1, lateral compression type 2, lateral compression type 3.
2. Patients between 18 and 80 years of age, inclusive.
3. Patient has reached skeletal maturity.
4. The patient's pelvic fracture is a result of trauma (includes polytraumatized patients).
5. The patient/family/guardian is English-speaking.
6. The patient's surgeon agrees to randomization (the patient is amendable to either operative or non-operative treatment).
7. Patient enrollment and, if applicable, patient randomization, can occur within 96 hours post injury.

Exclusion Criteria:

Patients who satisfy any of the following exclusion criteria will be ineligible for enrollment in the study:

1. The patient has prior surgical hardware in place that precludes intervention.
2. If the patient's pelvic fracture is classified as LC1 and the associated sacral fracture is incomplete as indicated by failure to violate both the anterior and posterior cortex.
3. The patient received prior surgical intervention for his/her current pelvic injury.
4. The patient has sacral morphology that precludes percutaneous fixation.
5. The patient is non-ambulatory due to an associated spinal cord injury.
6. The patient was non-ambulatory pre-injury.
7. The patient is currently pregnant.
8. The patient is enrolled in another study that does not allow co-enrollment.
9. The patient is likely to have severe problems maintaining follow up.

ADJUDICATING ELIGIBILITY

To ensure consistency in the application of inclusion criteria and in the classification of injuries, all fractures will be re-evaluated by a surgeon in Shock Trauma who is not treating the patient. These evaluations will be based on slides of AP and lateral x-rays. Each case will be independently reviewed. The non-treating surgeon will convene to discuss the case if there is disagreement regarding eligibility or classification of the injury to resolve differences of opinion.

CO-ENROLLMENT GUIDELINES

If allowed by the local IRB, participants in the Pelvis RCT study may be co-enrolled in other research studies based on the following guidelines:

A. Regardless of whether the participant is enrolled in the randomization arm or the observational arm of the Pelvis RCT study, the participant may be co-enrolled in any other observational study.
B. If the participant is enrolled in the randomization arm, he or she may only be co-enrolled in up to two additional randomized control trials prior to the completion of the intervention.
C. If the participant is enrolled in the randomization arm, he or she may co-enrolled in any other randomized control trial after the intervention is complete.
D. If the participant is enrolled in the observational arm, he or she may be co-enrolled in any other randomized control trial at any time.

RECRUITMENT

Approximately 130 participants will be enrolled in the Pelvis RCT study. Participants will be recruited during the index hospitalization for the treatment of a qualifying lateral compression type pelvic injury. Consenting procedures are described in detail in the Study Schedule and Informed Consent Sections of this protocol.

STUDY TREATMENTS

Both treatment options used in the study are current standard of care practices and the same resources (pain management, social work, physical therapy, etc.) will be available to study patients as to all trauma patients.

Non-operative Treatment Group

Patients enrolled in the non-operative treatment group will not undergo surgical intervention for their pelvic fracture. They will mobilize as per the surgeon's instructions according to standard of care of for this injury. X-rays will be taken at follow-up clinic appointments to determine if the injury is healing properly or if the pelvis has shifted and may warrant surgical intervention. If complications arise and/or surgery is required, crossover will be allowed and recorded within study follow-up forms.

Operative Treatment Group
Patients enrolled in the operative treatment group will undergo surgical intervention for their pelvic fracture. The surgeon will decide the best surgical technique as per standard of care for the patient's injury. The patient will mobilize as per the surgeon's instructions and x-rays will be taken at follow-up clinic appointments to determine if the injury is healing properly. If additional surgery is required or other complications arise, this will be recorded within the study follow-up forms.

CLINICAL EVALUATION

A summary of the clinical evaluations is outlined below and can also be found in Appendix B.

Medical Record Review
During the index hospitalization, information about the participant (medical history, height and weight, etc.) and the participant's injuries and hospital stay will be collected, including mechanism, presence of and severity of other orthopaedic and non-orthopaedic injuries, procedures done in the hospital, overall (and ICU) length of stay, time to mobilization (bed to chair) in physical therapy, pain medication administration, and discharge disposition.

Assessment of Study Injuries
The extent and severity of the pelvic injury will be prospectively assessed by the treating surgeon after initial x-rays are taken. The following injury characteristics will be collected:
- Lateral compression type classification of the pelvic fracture
- Skin defect associated with the pelvic injury
- Muscle and tendon injury associated with the pelvic injury
- Deep vein injury associated with the pelvic injury
- Nerve injury associated with the pelvic injury

Assessment of Study Injury Treatment
For participants undergoing operative treatment, the following information will be obtained:
- Type of fracture stabilization
- Type and timing of fixation revisions
- Limb Complications (type, severity, treatment)

Assessments at 2 weeks, 6 weeks, 3 months, and 1 year post injury
- Complications since last follow-up (type, severity, treatment)
- Assessment of fracture healing
- Weight bearing status and ambulation
- Use of ambulatory devices
- Pain assessment
- Narcotic use assessment

X-rays
AP and lateral x-rays at admission, post-operative treatment (when applicable), and at the 2 week, 6 week, 3 month and 1 year follow-ups will be obtained. These x-rays are obtained per standard of care.

PARTICIPANT INTERVIEWS

A summary of the participant interviews performed are outlined below and can also be found in Appendix D.

Baseline Hospital Interview
During the index hospitalization, participants will be asked about the following:

- Age, gender, race and ethnicity, and education
- Smoking history
- Previous injuries (specifically pelvis or back)
- Pain medication usage prior to this injury
- Work and health status prior to this injury
- General and pelvic function prior to this injury

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Follow-up Interviews
At 2 weeks, 6 weeks, 3 months, and 1 year following their injury, participants will be asked about the following:

- Any re-hospitalization or outpatient surgery since the last visit for any reason related to his/her pelvic injury
- Rehabilitation received
- Pain medication usage
- Work Status – Work Productivity and Activity Impairment
- Pain – Brief Pain Inventory
- Health Status – VR-12
- Pelvic Function – Majeed Pelvic Score

STUDY SCHEDULE

Screening and Consent
All patients between the ages of 18 and 80 (inclusive) with a lateral compression type pelvic fracture will be screened for eligibility by the research coordinator or research team members in close coordination with the surgeon investigators. Screening will typically occur within the first day after hospital admission. An eligibility checklist form will be completed on every potentially eligible participant and entered onto the electronic data capture system. The treating surgeon will be available via pager to answer questions regarding study eligibility. When the treating surgeon is not available, the study PI will be available to page. Contact information for the PI and alternate contact is available in Appendix A. In most cases, questions should be resolved at this level.

Once eligibility has been confirmed, the informed consent process will be completed by the research coordinator or research team member and attending surgeon. Patients will be approached about potential participation in the study as soon as is feasible following determination of eligibility. It will be important to enroll these participants as soon as possible to prospectively collect information about their injury and its treatment.

Following completion of informed consent, the participant's study injury characteristics will be further adjudicated by a non-treating surgeon as described in the Adjudicating Eligibility Section of this protocol. Participants with injuries that are not judged eligible for inclusion will be withdrawn from the study.

Enrollment/Baseline
Once consented into the study, baseline data regarding participant characteristics, injury characteristics, fracture classification and medical history/co-morbidities will be collected. Characteristics about the hospital course and treatment received will also be collected. A brief interview will be conducted with the participant. All data will be recorded on the paper Case Report Form (CRF) and entered into the electronic data capture system.

Follow-up
Participants will return for follow-up visits at 2 weeks, 6 weeks, 3 months, and 1 year post injury. Participants will undergo a clinical evaluation by the treating surgeon and be interviewed by the research coordinator or research team member. These visits tend to mirror clinic visits per standard of care, however there may be some circumstances where patients are unwilling to return to the clinic. In these situations the research coordinator or research team member may obtain as much visit data as possible by phone and/or medical record review to prevent loss of important study information. All data will be recorded on the paper Case Report Form (CRF) and entered into the electronic data capture system.

Retention
Every effort will be made to retain participants in the study. We will keep participants engaged through use of study updates during non-study clinic appointments, and reminder calls/letters for upcoming appointment visit window timeframes.

Visit Windows
Each visit will have an interval of time 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 approximately 1 week before or after the ideal date for the 2 week and 6 week follow-up appointments, and 2 weeks before or after the ideal date for a visit for the 3 month and 1 year follow-up appointments. Study data will still to be collected even if the visit falls out of the ideal window of time.

ASSESSMENT OF SAFETY

The study will monitor and report adverse events to ensure participant safety. Each participating site is responsible for ensuring that all local IRB requirements for reporting adverse events (both internal and external) are met.
The safety monitor (SM) is responsible for providing medical guidance and overseeing participant safety for the study. The SM participates in determining the course of action necessary to meet safety goals and objectives. This is achieved through the review of Serious Adverse Event reports; resolving safety issues; and interacting with the Principal and Sub-Investigators at each site.

Reportable New Information (RNI)
The following information must be reported to the coordinating center IRB within FIVE (5) business days of the investigator becoming aware of the information (please note that a separate RNI must be completed and submitted for each problem/event/report):

- Information that indicates a new or increased risk. For example:
    - New information (e.g., an interim analysis, safety monitoring report, publication in the literature, sponsor report, or investigator finding) indicates an increase in the frequency or magnitude of a previously known risk, or uncovers a new risk
    - An investigator brochure, package insert, or device labeling is revised to indicate an increase in the frequency or magnitude of a previously known risk, or describe a new risk
    - Withdrawal, restriction, or modification of a marketed approval of a drug, device, or biologic used in the research protocol
    - Protocol violation that harmed subjects or others or that indicates subjects or others might be at increased risk of harm
    - Complaint of a subject that indicates subjects or others might be at increased risk of harm or at risk of a new harm
    - Any changes significantly affecting the conduct of the research
- Any harm experienced by a subject or other individual which in the opinion of the local investigator is unexpected and at least probably related to the Human Research procedures and suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized
    - A harm is “unexpected” when its specificity or severity are inconsistent with risk information previously reviewed and approved by the IRB in terms of nature, severity, frequency, and characteristics of the study population
    - A harm is “at least probably related to the Human Research procedures” if in the opinion of the local investigator, the research procedures more likely than not caused the harm (greater than 50% probability)
- Non-compliance with the federal regulations governing human research or with the requirements or determinations of the IRB, or an allegation of such non-compliance
- Failure to follow the protocol due to the action or inaction of the investigator or research staff
- Breach of confidentiality
- Change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a subject

- Incarceration of a subject in a study not approved by the IRB to involve prisoners
- Complaint of a subject that cannot be resolved by the research team
- Premature suspension or termination of the research by the sponsor or the investigator
- Unanticipated adverse device effect (any serious adverse effect on health or safety or any life-threatening problem or death caused incidence in the investigational plan or application – including a supplementary plan or application – or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects)
- Audit, inspection, or inquiry by a federal agency
- Written reports of study monitors

Serious Adverse Event (SAE)
Serious Adverse Events may be discovered during regularly scheduled visits or though unscheduled participant contacts between visits. SAEs will be managed according to the medical judgment of the treating physician and source documentation will be maintained (e.g. laboratory and/or radiology reports, clinical notes, discharge summaries). The following are the categories considered for a serious adverse event and must be reported to the IRB during the continuing review process:

- Serious, unexpected, not related
    - Is unexpected, in terms of nature, severity, or frequency, given the research procedures that are described in the protocol and informed consent document and the characteristics of the participants eligible for the study
    - e.g. Death not due to study participation
- Serious, expected, related
    - Is related or possibly related to treatment/procedures under study; possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the study procedures or treatments
- Serious, expected, not related

Study patients who experience an SAE will be followed until resolution of the event and a final report will be submitted to the safety monitor and IRB. Please note that SAE's and RNI's may overlap and a single event may be classified under both conditions.

DATA ANALYSIS

Our primary hypothesis is that the operative treatment group will have lower VAS pain scores compared to the non-operative treatment group both during their hospital stay and in the short-term outpatient follow-up.

Based on the results of a pilot study, we expect pain scores in the non-operative group to have a mean of 5.7 and a standard deviation of 2.3. Assuming a 20% reduction in pain scores, 130 patients (65 per arm) are required to have an 80% chance of detecting, as significant at the 5% level, a decrease in the primary outcome measure from 5.7 in the control group to 4.56 in the experimental group. This is our primary outcome and the study will be powered for this variable.

Primary data analysis will involve direct comparison of the change in value of the reported pain scores at the time points listed below. We will be powered to detect a 20% reduction in pain. Secondary analysis will compare the value of narcotics administered at the distinct time periods. Tertiary analysis will be comparing the time (in days) to mobilization with physical therapy. The previous retrospective pilot study incorporated a propensity factor, generated from well documented sources of pain. As this is a prospectively randomized trial, we do not anticipate needing to accommodate for matching.

RANDOMIZATION

Eligible patients will be randomized in equal proportions to one of the two treatment groups: 1) operative treatment of the lateral compression type fracture, 2) non-operative treatment of the lateral compression type fracture. Allocation will be concealed using a centralized 24-hour computerized randomization system, www.randomize.net, that will allow Internet based allocation. The treatment allocation will be stratified on the following prognostic factors to ensure balance between the intervention groups: 1) patient intubation status at time of enrollment, 2) patient prescription pain medication usage during the month prior to injury.

DATA MANAGEMENT

Data will be collected in real time by the study site investigator, research coordinator, or research team member, directly on paper Administrative Forms (AFs) or Case Report Forms (CRFs) which will serve as source documents for the study. The study personnel will obtain the information necessary to complete the case report forms (CRFs) from several sources including but not limited to, the patient's medical record, clinical evaluations and patient interviews. These forms will NOT contain the patient's name, SSN, or hospital medical record number; they will be identified only by a unique patient-specific study number. All data requested on the AF or CRF must be completed. Source documents will be signed by the study team member that has reviewed the AF or CRF. An electronic data capture system, REDCap, will be used to submit data to the coordinating center located at University of Maryland, Shock Trauma. Upon receipt of the data, the coordinating center will make a visual check of the data and will query all missing data, implausible data, and inconsistencies.

The REDCap data entry screens will be similar to the paper AFs and CRFs. Data integrity will be enhanced by using the electronic data capture system through a variety of mechanisms for checking data at the time of entry including referential data rules, valid values, range checks, and consistency checks against data already stored in the database. Clinical site personnel will be able to view and modify data for participants recruited from their clinical site only. Each time data is submitted or modified, it will be validated by the coordinating center.

All AFs and CRFs must be kept secure in locked cabinets or other enclosures that are accessible only to study personnel. All electronic data must be password-protected and accessible only to study personnel. The coordinating center will be responsible for backing up all electronically submitted data. Hard copy documents containing subject data and patient identifiers (and contact

information) will be stored in secure document containers (file cabinets, lockers, drawers, etc.) in accordance with standard document management practices. Paper forms and the files containing personally identifiable data at each site will be destroyed within 5 years of study completion.

Quality control quality assurance procedures will be in place for the duration of the study. Ongoing data edits and internal audits will be performed to ensure collection of quality data. The continuous and timely flow of data from the AFs and CRFs to the REDCap electronic data capture system is an essential prerequisite for maintaining data quality.

Monthly performance reports will be completed by the coordinating center research coordinator summarizing among other things: recruitment, status of follow up, data completion, and timelines of data entry.

Missing data queries will be reported on the monthly basis by the research coordinator. The research team will be asked to answer these queries as soon as possible. Any unresolved queries will continue to be reported on the monthly basis.

MISSING DATA

As with most prospective studies, missing data will be unavoidable, even with excellent follow up. Since the informative nature of missing data cannot be verified from the observed data, we will adopt a sensitivity analysis framework for reporting results. We will analyze data under a variety of modeling assumptions regarding how strongly the missingness mechanism is related to outcomes. Regarding study conduct, we will:

1. Limit participant burden and inconvenience in data collection
2. Select high quality research team members
3. Monitor and report missing data rates during the study
4. Emphasize the importance of full participation in the study during the consent process
5. Collect information on the reasons for missing data
6. Actively engage participants in the study and educate them about the importance of their engagement
7. Collect surrogate information on participants who miss clinic visits
8. Hold regular meetings to discuss strategies for enrollment and engagement of participation

While these efforts will help to minimize missing data, we recognize that missing data is inevitable.

RESEARCH ETHICS APPROVAL

This protocol, the consent form template, the AFs, and the CRFs have been reviewed and approved by University of Maryland Institutional Review Board (IRB). The protocol, clinical site-specific informed consent forms, and any participant recruitment material will need to be reviewed and approved by each clinical site's local ethics board. Prior to commencement of the

study the clinical site must provide the coordinating center with a copy of the ethics board approval.

INFORMED CONSENT

Both a Randomized Control Trial (RCT) consent and Observational (OBS) consent has been prepared for the Pelvis RCT study and is attached in Appendix C. The consent form describes 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.

Eligible patients will be approached for their consent to participate. Informed consent will be obtained prior to treatment group assignment.

To encourage a high level of participation from eligible patients, the attending surgeon will be involved in the consent conversation. The conversation will be initiated by the research coordinator or research team member and the surgeon together. Patients and their families will be informed of the risks and benefits of participation and what will be expected of them if they choose to participate. Consent will be obtained in accordance with principles of GCP and ICH guidelines.

The study should be presented as a randomized control trial upon initial consent conversation. If the patient or LAR declines to participate after full understanding of the trial, only then should the observational arm be presented.

Whenever possible, the patient him or herself (as opposed to a proxy) should be consented. Prior to initiating the consent process, a research team member will determine if the patient has the ability to understand the relevant study information and communicate and maintain a choice. If it is determined that the patient lacks the capacity to consent, the legally authorized representative (LAR) will be contacted.

The research staff will endeavor to answer all questions posed by the participant and his/her family to ensure their understanding of the protocol. A limited number of questions will be asked of all patients after they are introduced to the study and have reviewed the consent form. These questions assess the person's understanding of the study and what it means to participate, their appreciation of the consequences of participation, and their ability to consider alternatives to participation. A formal comprehension test may be utilized, or comprehension will be assessed by the person(s) obtaining the consent. A template for a comprehension test is provided in Appendix D.

The research team member will ask the questions and determine the appropriateness of the responses. If the research team member is at all unsure about the patient's ability to consent s/he will consult with the PI.

A legally authorized representative (LAR) with reasonable knowledge of the potential participant will be approached to consent on the patient's behalf if one of the following is true:

- The patient is unresponsive or intubated (and likely to remain unresponsive or intubated before surgery or 96 hours post-injury)
- The patient cannot adequately answer the questions and it is determined that the patient's level of cognition is not likely to change before surgery or 96 hours post-injury

The choice of LAR will follow standard procedures. In order of priority the following will be approached:

- Health care agent (identified under a written advance directive)
- Court appointed guardian
- Spouse
- Adult child
- Parent
- Adult brother or sister
- Close friend or other relative

Guidance will be provided to assist the LAR in making the consent decision. They will be advised to base the decision on the patient's expressed wishes, or, if these are not known, what they believe the patient would have desired under the circumstances of the injury, his or her beliefs and values. If the LAR does not know what the patient would have wanted, the LAR will be advised to base the decision with the patient's best interest in mind. They will be asked to carefully consider how much leeway the patient would likely give the LAR in making the choice about participation in the study. When the participant regains capacity to consent during the study period, the participant will be re-consented using standard consenting procedures described above.

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.

VULNERABLE POPULATIONS

The study will not include children, pregnant women, or prisoners.

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.

Participants will be identified only by an identification code but not by their name, SSN, or hospital medical record number. The Research Coordinator will maintain a separate confidential

enrollment log which matches identifying codes with patient names and addresses available only to research staff.

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 IRB or Safety Monitor. Consent procedures and forms, and the communication, transmission and storage of patient data will comply with the IRB and requirements for compliance with the Health Insurance Portability and Accountability Act (HIPAA).

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.

REPORTS

The site research coordinator will respond to all site queries and progress reports monthly to ensure quality data collection and address missing data or visits at regular intervals.

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, paper forms will be shredded and the file containing personally identifiable data will be permanently deleted from local site computers.

SUPPORTING LITERATURE

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APPENDIX A: STUDY CONTACT ROSTER

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APPENDIX B: DATA COLLECTION SCHEDULE

Assessment	Screen / Enroll	Pre-Rand. Base	Post-Rand. Base	96-hour	2 week	6 week	3 month	1 year
Pelvic x-rays	X							
Informed Consent	X							
HIPAA	X							
Stratification Levels (AF03)								
Intubation Status (at time of consent)		X						
Prescription Pain Medication Usage (during month prior to pelvic injury)		X						
Patient Intake (CRF01)								
Demographics (age, gender, race/ethnicity, education)			X					
Smoking History			X					
Previous Injuries			X					
Pre-injury Pain Medication Usage			X					
Pre-injury Work Status (WPAI:SHP)			X					
Pre-Injury Health Status (VR-12)			X					
Pre-Injury Pelvic Function (Majeed Pelvic)			X					
Index Hospitalization - Clinical Intake (CRF02)								
Length of Stay & Discharge Disposition			X					

Assessment	Screen / Enroll	Pre-Rand. Base	Post-Rand. Base	96-hour	2 week	6 week	3 month	1 year
ICU Length of Stay			X					
Date/Time & Mechanism of Injury			X					
Height & Weight			X					
Medical History			X					
Time to Mobilization (Bed to Chair)			X					
Narcotic Use			X					
OR Trip(s) Identification			X					
Classification of All Injuries			X					
Study Injury Characteristics			X					
Study Treatment Characteristics			X					
Patient Follow-Up (CRF03 & CRF04)								
Brief Pain Inventory (BPI)				X	X	X	X	X
Re-hospitalizations or Surgeries					X	X	X	X
Physical Therapy Tracking					X	X	X	X
Post-Injury Pain Medication Usage					X	X	X	X
Post-Injury Work Status (WPAI: SHP)					X	X	X	X
Post-Injury Health Status (VR-12)					X	X	X	X
Post-Injury Pelvic Function (Majeed Pelvic)					X	X	X	X
Clinical Follow-Up (CRF05)								
Ambulation & Weight Bearing Status					X	X	X	X
Pain Medication Usage					X	X	X	X
Fracture Healing Status					X	X	X	X
Complications (type, severity, treatment)					X	X	X	X

APPENDIX C: CONSENT TEMPLATES

See attachment.

APPENDIX D: AFs and CRFs

See attachment.