Fracture Table vs. Lateral Positioning for Intramedullary Fixation of Femur Fractures (The FLiP Study): A protocol for a pilot randomized controlled trial

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Background: Femoral Shaft fractures are devastating and life threatening injuries. Femoral shaft fractures are most commonly treated with intramedullary fixation. Malrotation of the injured limb after fixation is a common and significant complication following femoral shaft fractures. During the operation, patients can be positioned either supine or in a lateral position. Additionally, patients can be placed on a standard radiolucent operating room table, or placed on a fracture table with traction statically applied to the operative limb throughout the case. Previous case series and cohort studies have shown equivalence between study groups, but choice between positioning options remains controversial. Methods: This represents a protocol for a randomized controlled pilot trial. We will be compared lateral positioning with use of manual traction to supine positioning with use of a fracture table. Primary outcomes will be in assessment for feasibility for a future full scale randomized trial, including evaluating patient recruitment, patient compliance with followup, contamination between treatment arms and others. Results: The primary outcome will be feasibility for a future trial. Secondary outcomes will include malrotation as measured through intraoperative radiographs, postoperative computed tomography scans and gait analysis at 6 months.

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Abstract

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Methods: This represents a protocol for a randomized controlled pilot trial. We will be compared lateral positioning with use of manual traction to supine positioning with use of a fracture table. Primary outcomes will be in assessment for feasibility for a future full scale randomized trial, including evaluating patient recruitment, patient compliance with followup, contamination between treatment arms and others.

Results: The primary outcome will be feasibility for a future trial. Secondary outcomes will include malrotation as measured through intraoperative radiographs, postoperative computed tomography scans and gait analysis at 6 months.

Introduction

Femoral shaft fractures are common and severe injuries that typically occur alongside other complex, high-energy injuries in the poly-traumatized patient. Femur fractures can yield extensive bleeding and muscle injury of the thigh, and have a high worldwide burden; occurring at a rate between 14 and 42.5 /100,000 person years, with approximately 1 in 10 road traffic accidents worldwide involving a femoral shaft fracture treated by surgery[1]. Additionally, there is a significant disparity of burden for diaphyseal femur fractures, with 91% occurring in lower middle class income countries, with the majority affecting younger males.[2]

To help mitigate the effects of ongoing blood-loss, worsening inflammation and pain from the unstable fracture ends, femoral shaft fractures require urgent management using either an early total-care or damage-control orthopaedics approach[3,4,5]. Associated injuries, markers of resuscitation, and overall patient stability guide operative decision making on timing of surgical intervention[6]. Definitive internal fixation using reamed, locked intramedullary nailing (IMN) has become the standard of care in the adequately resuscitated patient[7] as it provides fracture stability while facilitating nursing care and patient mobilization[8,9]. Multiple femoral IMN techniques exist, however most femoral shaft fractures can be treated with an antegrade nail using either supine (fracture table) or lateral (free-leg drape) positioning[10,11]. Fracture pattern, patient characteristics, associated injuries, hospital-resources, availability of assistants and surgeon preference may all play a role in determining which positioning option is chosen. There are advantages and disadvantages to each, and little clinical evidence exists to aid in decision-making.

This research group completed a systematic review of the literature on patient positioning during antegrade nailing of femur fractures in the last year (Journal # OTAI-18-00048). The review revealed only three non-prospective studies on this specific topic,[12,13]. This clearly leaves much uncertainty surrounding optimal patient positioning during the definitive treatment of these critical injuries.

For antegrade IMN, supine positioning is most commonly accompanied by a fracture (or traction) table. This surgical table secures the injured extremity and maintains it in a set position throughout the procedure using an adjustable amount of mechanical traction applied though a boot or skeletal traction pin, while using posts and straps to provide counter traction. While this may do an excellent job at obtaining length, it may be easy to mal-reduce comminuted fractures if keen attention is not paid to other anatomic reference points that help restore alignment and rotation[14]. This is vital, as the main reason for malpractice litigation following a femoral shaft fracture is failing to restore anatomic length, alignment and rotation[15]. While the traction table may be a useful tool, it can easily over-power the patients own resting soft tissue tension, and

lead to mal-reduction of the fracture. The most challenging intraoperative assessment is that of femoral rotation[16]. Numerous tools are used, including cortical width, cortical diameter, lesser trochanter profile and others[17]. The most reliable technique described in recent papers is the lesser trochanter profile, but it requires a true anteroposterior view of the pelvis, which can be challenging to obtain with the fracture table in situ.

In addition to this, numerous issues may arise secondary to prolonged procedures and application of traction. Flierl described a host of potential issues: perineal skin and soft tissue compromise from using a metal post between the patients leg, neurologic impairment of the non affected leg with either a femoral or peroneal nerve palsy, and iatrogenic compartment syndrome of the non affected extremity[18]. All of these can occur at a variable rate, but are serious and potentially avoidable complications. Lastly, not every hospital has easy access to a fracture table. They are expensive, routinely over $200,000 including all orthopaedic extensions[19], and are specialized tables designed exclusively for orthopaedic trauma. Fracture tables may not be a feasible or practical piece of equipment for some centers to invest in.

The use of the lateral position for intramedullary nailing has been described for the past thirty years[20], though rarely reported on in the literature. Patients who present with femur fractures are often multiply injured trauma patients, and as such surgeons and anaesthesists have been hesitant to place these patients in a lateral decubitus or even a modified lateral position, with a bump under the patients hip, in the past. Their concerns stem from belief that a lateral position can worsen respiratory function and prolong extubation, leading to longer ICU stay, especially in patients who may have had thoracic injuries during their index traumatic event. However results from the most recent cohort studies actually suggest the opposite, that patients treated in the lateral position may have shorter ICU stay and reduced days on a ventilator, adjusting for patient risk in propensity based analyses[21].

Furthermore, part of the reluctance to use the lateral position may be due to lack of surgeon experience and comfort. The commonly used technique of using the fracture table for femoral neck fractures and intertrochanteric hip fractures is easily applied for fixation of femoral shaft fractures. Converting the patient position to the lateral position yields a different radiologic perspective throughout the case and may represent a challenge for surgeons who are not accustomed to interpreting intraoperative fluoroscopic images in this position.

In order to ascertain surgeon preferences, we conducted both a province wide survey through the Ontario orthopaedic association (OOA), Canadian Orthopaedic association (COA) and an international survey amongst members of the AO Trauma group. The 197 respondents clearly showed the disparity and disagreement amongst standard of care for these significant

injuries. Sixty four (64) percent of surgeons surveyed in the AOT group said they prefer either sloppy lateral or direct lateral for antegrade fixation of femur fractures (AFFF). Interestingly, they reported that their colleagues, perhaps not members of the AOT, choose supine on a fracture table for AFFF more than 65% of the time. Commonly, surgeons reported that lack of comfort and expertise (48.2%) were reasons for themselves not choosing a lateral position for AFFF. Furthermore, the respondents endorsed the significant complication risk of fracture table use, with 82% of respondents answering that they witness a traction table related injury at a rate greater than 1%. Lastly, 60% of respondents were interested in being part of this clinical trial, indicating the interest in and controversy surrounding this topic. This topic was also presented at the Orthopaedic Trauma Association meeting (OTA), in the Canadian Orthopaedic Trauma Society (COTS) subgroup meeting. Again, there was substantial interest in this topic, and suggestions from that meeting were incorporated as modifications to the study protocol.

Respondents reported that the main benefits of lateral positioning were ease of control of the fracture fragments throughout the entire procedure, as the leg is not under constant traction or draped outside of the sterile field. This finding has been reproduced when use of manual traction in a supine position has been compared to fracture table in a prospective randomized study, but never objectively assessed with a laterally positioned patient.[22] This allows the fracture fragments to be freely manipulated and muscles to find their resting tension, which may help better restore overall alignment. Furthermore, the use of the lateral position does not yield any traction related complications.

Materials & Methods

STUDY DESIGN

Design Overview and Rationale

This will be a 2-group parallel-randomized controlled pilot trial. This design will allow us to have direct evidence comparing the efficacy and safety of the two surgical interventions. We require a pilot trial prior to a large multi-centre definitive trial to identify any issues with the methodology, study process, enrollment, data collection, and participant retention and to make any necessary changes prior to large-scale implementation of a definitive trial.

Setting

The Centre for Evidence-Based Orthopaedics (CEO) at McMaster University in Hamilton Ontario will be the Methods Centre for this trial. The CEO has conducted several of the largest multinational trials and observational studies in orthopaedics to date including the 1319 patient SPRINT trial, the 2447 patient FLOW trial, the 2945 patient PRAISE study, the 1108 patient FAITH trial, the 1501 patient HEALTH trial, and the ongoing INORMUS study that has enrolled more than 30,000 patients to date. The CEO has the infrastructure to successfully conduct large multicentre studies including research coordinators, data managers, statisticians/data analysts, a large network of investigators, and available hardware, software, and office space. Additionally, McMaster University is widely known for innovations in evidence-based medicine, clinical epidemiology, biostatistics, and health research methodology. Our interdisciplinary research team is comprised of experts in orthopaedic surgery, anaesthesia and pain management, health research methodology, and biostatistics, and includes patient advocates.

Pilot sites will include the Hamilton General Hospital in Hamilton, Ontario, and possibly other academic centres affiliated with the Canadian Orthopaedic Trauma Society (COTS). This will be determined by funding available at respective local centres. Hamilton General Hospital is a Level One trauma centre serving all municipalities east of Oakville in the greater Toronto area, as well as throughout the southern part of the golden horseshoe including Hamilton, Haldimand-Norfolk, Niagara, Brantford, and Burlington. This hospital treats between 6-10 mid shaft femur fractures per month (determined through internal database review).

Eligibility

Inclusion Criteria

- Adult (18+)
- Mid shaft (Diaphyseal) femur fracture appropriate for antegrade fixation
- Surgeon agreement for participation in study
- Ability to obtain perioperative imaging (CT scans)
- Provision of informed consent

Exclusion criteria

- Inability to provide informed consent (e.g. cognitive disability, language barrier)
- Age > 65
- Bilateral Femoral Fractures
- Inability or lack of willingness to attend follow up

- Ipsilateral tibial fracture
- Ipsilateral femoral neck fracture
- Ipsilateral acetabular fracture
- Pregnant or breastfeeding
- Contraindications to CT imaging including impaired kidney/liver function, or lack of timely availability
- Periprosthetic fracture
- Pathologic fracture
- Significant delirium or dementia

Screening and Consent Process

Enrolling surgeons or authorized research personnel will identify all potentially eligible patients who have diaphyseal femur fractures. Similar to the A-Prep study[23], we will use cluster randomization. This type of randomization implies that the patient will not be individually randomized but the institution would be. A positioning would be randomized at the first month of initiation and all patients with this injury will be operated using that position. The position will alternate on a monthly basis. All patients matching study criteria will undergo surgery either in lateral or supine positioning based on study month.

This allows for the patient to be approach for participation postoperatively. Patients will be approached after surgery. The trial will be explained to patients with emphasis that there will be no negative implications should they choose not to be involved. A standardized consent form will be provided to patients which will be signed and stored securely by the research coordinator. As part of the randomization, patients will also be randomized to inclusion or exclusion from gait analysis studies at one year, with 20% of patients participating in gait analysis. This second randomization will be done upon completion of follow up at one year and it would be included in the initial consent form. We will obtain ongoing consent from patients at every follow-up appointment and patients will have the option to withdraw consent. In order to do so, patients may inform their surgeon or any research staff. Patients will be provided with the research coordinator's contact information and may also withdraw consent by contacting the research coordinator directly at any time during the study period. At the 6-month follow up, patients will be notified of the 1-year gait analysis assessment. Consenting procedures will follow local policies and International Council on Harmonization and Good Clinical Practice (ICH-GCP) regulations.

Interventions

Supine Positioning, Fracture Table

The supine fracture table group will be positioned supine in the operating room, on a fracture table. The operative leg will be placed in a boot, attached to the traction limb. The non operative leg will either be scisorred away from the operating area in a traction boot (without traction placed), or placed in a stirrup at 90 degrees of hip flexion in hemilithotomy. A central post will be used to prevent patient movement during application of traction, and all bony prominences will be padded. Fluoroscopy will be obtained through standard practices.

Lateral Positioning, Free drape

The lateral positioning group will be placed in lateral position after anaesthetic has been provided. A beanbag will be placed below the patient, and the patient will be safely turned to a lateral position (Figure 1, Figure 2). The beanbag will be inflated, the leg will be prepped, and a free drape will be applied. No traction will be used. Alternatively, some participating sites may use stulberg positioners rather than an inflatable beanbag, based on hospital preference.

Adherence, Contamination, and Crossovers

In case of crossovers, patients will be analyzed in the group to which they were randomized (intention-to-treat).

Randomization

Following confirmation of eligibility, patients will be enrolled into the study group based on block randomization per site. To ensure there is minimal specialist bias, we will invite all provincial trauma surgeons to a cadaver course focusing on lateral patient positioning for AFFF. If the orthopaedic trauma surgeon on call has not performed at least three operations of antegrade IMN of femur fractures in the last year, or attended a cadaver-based course, then the patient will not be a candidate for the study.

We will aim for a 1:1 allocation ratio. **Figure 1** summarizes the screening and randomization process.

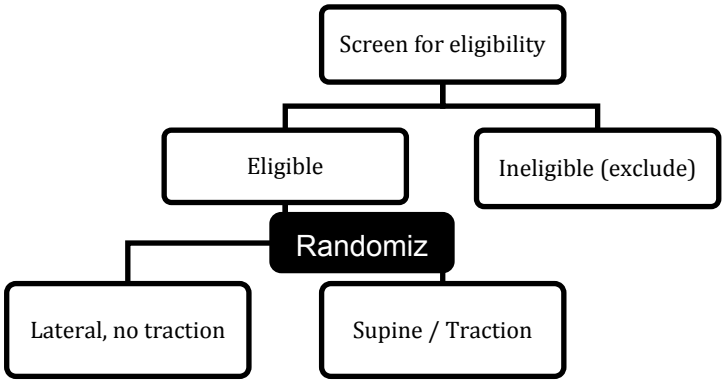


Figure 1: Summary of screening and randomization

Blinding

Patients will be blinded to the treatment protocol they are randomized to. The surgical team will not be blinded to the randomization. The outcome assessors, in particular the radiologists who assess post operative rotation and alignment of the femur fracture, will be blinded to which group the patients were allocated.

OUTCOMES

Primary Outcome

Our primary outcome for the pilot trial is feasibility, including the following:

- Recruitment rate
- Participant retention
- Data completeness
- Treatment compliance

Criteria for feasibility success

We will consider the pilot study to be a success if we are able to achieve the following:

- Recruitment of 80 % of the calculated 200 patients in two years (with an interval assessment of at least 60 patients within first 8 months)
- Follow-up of at least 90% of patients at 3 months
- At least 80% of questionnaires completed at 3 months

Secondary Outcomes

- Length, alignment and rotation of femur measured immediately post operatively through bilateral computed tomography scans by blinded personnel.
- Functional gait abnormalities as measured by gait analysis at one year
- Walking/Gait ability as measured by timed up and go test at 6 weeks, 3 months post surgery
- Pain at 2 weeks, 6 weeks, and 3 months post-surgery. Both pain in the operative leg, and generalized assessment of pain will be included.
- Range of motion 2 weeks, 6 weeks, and 3 months post-surgery
- Euroquol score at 3 and 6 months post operatively
- Satisfaction with pain control at 3 months post-surgery
- Systemic and local adverse events up to 3 months post-surgery including infection, need for revision, and need for hospital readmission

Measurement of Secondary Outcomes

Length, alignment and Rotation

Immediate (within 48 hours of surgery) post-operative bilateral computer tomography of the operated patients lower extremity will be completed. The radiology team, led by Dr. Mammen, will be involved in this study. The quoted cost per CT scan is $54 (CAD) per patient. This will be incorporated into the eventual budget. These will be reviewed and reported by a staff radiologist. Outcomes included length discrepancy, internal or external rotation of the femur compared to the longitudinal axis and mal-alignment or mal-reduction of fracture components will be recorded. If significant malrotation is identified, need for reoperation with patient will be discussed and recorded as a complication.

Additionally, the patient group will be assessed by functional assessment through timed up and go testing at 6 week, 3 month and one year follow up. Lastly, patients will undergo gait analysis at one year to compare their gait patterns to matched population controls. Population controls have been collected through the McMaster gait analysis lab during previous studies and data has been de-identified. Patients have previously consented to use their de-identified data for future studies. This will help to elucidate if there are relationships between gait abnormalities and patient positioning, radiologic malrotation or patient satisfaction.

Pain

We will use a modified version of the World Health Organization (WHO) definition of persistent post-surgical pain. The modifications are to add a minimum severity of pain. To meet the definition of PPSP, a patient mist experience all of the following:

- The pain is in the study extremity
- The pain began after surgery
- The pain has persisted for at least three months after surgery
- The pain is not better explained by an infection, malignancy, a pre-existing pain condition or any other alternative cause (as judged by the treating surgeon)
- The severity of pain must be at least 4 on an 11-point NRS for average pain in the past week

Wound Complication

We will assess the wound integrity at 2 week, 1 month and 6 month follow up. Any wound dehiscence, or concern with appearance or superficial infection will be documented, as well as requirement to treat with oral or parenteral antibiotics.

Satisfaction with pain control

We will ask patients to rate their satisfaction with pain control using a 5-point Likert scale with options ranging from “poor” to “excellent”.

Systemic and local adverse events

An adverse event (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study.

Study Visits and Timelines

Patients will be screened for eligibility and randomized at hospital admission. We will collect study data at the following timepoints:

- 2 weeks
- 6 weeks
- 3 months
- 1 year

All visits after the baseline visit can be completed in-clinic or by telephone with additional information collected from medical records, as needed. **Table 1** presents a summary of study events and measurements at each timepoint.

Table 1: Schedule of events

Study event/ measure	**Baseline (At admission)**	**In Hospital (post operative)**	**2 week f/u (10-18 days)**	**6 week f/u (35-49 days)**	**3 month f/u (77-105 days)**	**1 Year**
Screening	X					
Consent		X				
Randomization	X					
Demographics and baseline info		X				
Pain			X	X	X	x
Length, Rotation		X				
Adverse events	X	X	X	X	X	x
Satisfaction			X	X	X	x
Gait Analysis						X

Strategies for Enhancing Retention

We will use strategies adapted from Madden et al to maximize participant retention. Key aspects of our retention strategies include:

- The study visits are aligned with standard of care clinical visits for convenience
- The study was designed to strike a balance between collecting sufficient information and not overburdening patients
- Selection of clinical sites with experienced research personnel
- The protocol allows for flexibility in visit windows to minimize missed visits
- The methods centre will routinely monitor loss to follow-up and communicate with sites as needed
- Research personnel will collect multiple pieces of contact information from participants

- We will request permission to access patients' medical records to identify all adverse events
- Participants will only be deemed lost to follow-up until after the 6 month visit is due and after all exhaustive measures have been taken to locate the participant

Data Collection and Data Management

Clinical sites will be provided with the trial Case report forms (CRFs) prior to initiation of enrollment. Research personnel at each clinical site will submit the required data, as detailed on the CRFs, to the Methods Centre using the Research Electronic Data Capture (REDCap) system. Clinical site personnel will receive a unique login and password for the REDCap Cloud system and will be able to view and modify data for participants recruited at their clinical site. The REDCap Cloud system uses a variety of mechanisms for checking data at the time of entry including skip logic, range checks, and data type checks. Upon receipt of new data, the personnel at the Methods Centre will query all missing, implausible, or inconsistent data and clinical site personnel will be notified of open queries through regular quality control reports, and will be required to respond promptly. Methods Centre personnel will also conduct regular statistical monitoring of data, and periodic on-site and remote monitoring of data.

STATISTICAL METHODS

Sample Size

The sample size for the pilot trial is based primarily on feasibility objectives. We determined *a priori* that the study would be feasible if loss to follow-up is less than 10%. We believe that our loss to follow-up will be about 5%; therefore, using the confidence interval approach suggested by Thabane et al, we require 200 patients to achieve a 5% margin of error (which will generate a confidence interval that excludes 10%).

Statistical Principles

The analysis and reporting of results will follow the CONSORT guidelines for reporting of randomized pilot and feasibility trials. The process of participant enrolment and flow throughout the study will be summarized using a flow diagram. Participant demographics, medical history, surgical details, and peri-operative details will be summarized by treatment group using descriptive summary measures: expressed as mean, standard deviation and confidence

internvals (95%), or median and interquartile range for continuous variables, depending on the distribution, and number and percent for categorical variables. Statistical significance will be defined as a P value <0.05, and all statistical testing will be 2 – tailed. We plan to include the data from our pilot in the definitive trial if we are able to demonstrate feasibility and there are no important changes to our patient population, intervention, or outcome measures. All patients who are enrolled in the trial and randomized will be included in the analysis, regardless of level of adherence to the intervention, or any other deviation from protocol. We will not impute for missing data in this pilot trial.

Primary Analysis

Point estimates of recruitment and feasibility events, including adherence to protocol and follow-up rate at one-year, as proportions with 95% CIs will be presented. The pilot study results will be evaluated to identify recruitment issues, data management issues, and inform anticipated follow-up rates.

Subgroup Analyses

We will not conduct any subgroup analyses in the pilot trial. If relevant, we may consider subgroup analyses for the definitive trial.

Interim Analysis

We will not conduct an interim analysis for the pilot trial. We will not stop the trial for benefit, and we will consider advice from the Data and Safety Monitoring Committee (DSMC) regarding stopping for harm.

TRIAL ORGANIZATION

Principal Investigator

The Principal Investigator (PI) and Co-Principal Investigators (Co-PIs) are responsible for overall study design and conduct. The Steering Committee, Advisory Cores, and DSMC will provide advice to the PI and Co-PIs regarding trial design and conduct and the PI and Co-PIs will be responsible for making decisions based on their advice. The PI and Co-PIs will also be responsible for training and overseeing Methods Centre personnel, and ethics and regulatory submissions.

Steering Committee and Advisory Cores

The Steering Committee and Advisory Cores are responsible for providing guidance and advice regarding clinical, methodological, statistical, and practical aspects of the study design and conduct. The Steering Committee will be comprised of a Steering Committee Chair, a Methods Core, a Clinical Advisory Core, and a Patient Advisory Core. The Methods Core will consist of methodologists and statisticians who will ensure scientific rigor of the trial. The Clinical Advisory Core will consist of orthopaedic surgeons, pain experts, and other clinical experts as needed to ensure applicability to the clinical areas of interest. The Patient Advisory Core will consist of at least two patients who have experience with this type of injury to ensure applicability and relevance to patients.

Methods Centre

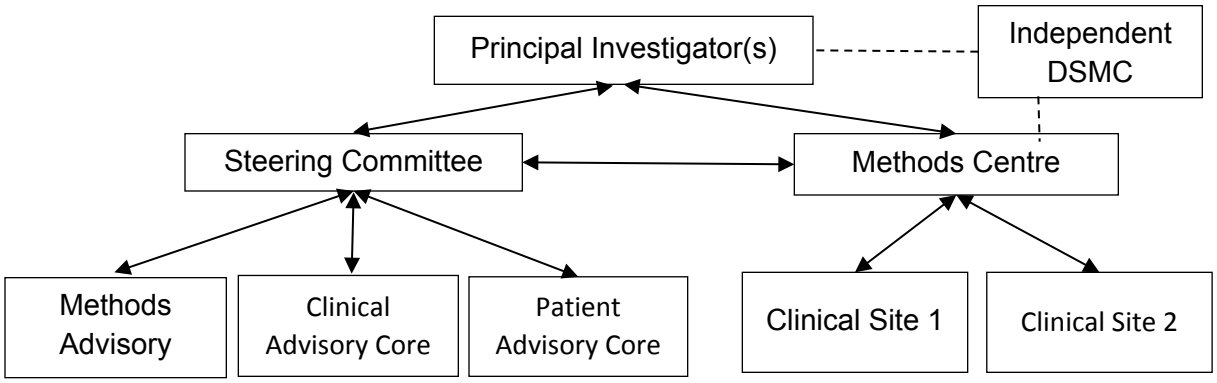
The Methods Centre, under the direction of the Principal Investigator and Co-Principal Investigators, are responsible for trial management, logistics, and execution. The Methods Centre will be the primary correspondent between the PI/Co-PIs, clinical sites, and committees.

Clinical Sites

The clinical sites are responsible for screening, enrolling, randomizing, and following patients according to the study protocol. They will also be responsible for communicating regularly with the Methods Centre to resolve any data queries and quality control issues and communicate adverse events in a timely manner.

Data and Safety Monitoring Committee

This trial will have a formal Data and Safety Monitoring Committee (DSMC) that is independent of the study investigators. The DSMC's role is to regularly assess safety reports and the progress of the trial and provide advice to the Principal Investigator and Steering Committee regarding continuation of the trial and other patient safety and data quality issues. The DSMC is comprised of three members including a biostatistician (DSMB chair), a pain expert, and an orthopaedic surgeon.



ETHICS AND DISSEMINATION

This study will be conducted according to international standards of ICH-GCP, applicable government regulations, and institutional research policies and procedures.

Research Ethics Approval

The Methods Center at McMaster University will receive ethics approval from the Hamilton Integrated Research Ethics Board (HiREB) prior to the distribution of this protocol and any approved study materials to participating clinical sites. Each participating site will also receive ethics approval prior to trial initiation.

Confidentiality

- Information about study participants will be kept confidential and managed in accordance with the following rules:
- All study-related information will be stored securely
- All study participant information will be stored in locked file cabinets within locked offices accessible only to study personnel
- All paper and electronic CRFs will be identified only by an anonymized participant ID code
- All study databases will be password-protected

Communication, transmission and storage of patient data will comply with the applicable ethics committee. In the event that a participant revokes authorization to collect or use personal health information, the participating clinical site retains the ability to use all information collected prior to the revocation of participant authorization. For participants who have revoked authorization to collect or use personal health information, attempts should be made to obtain permission to

collect at least vital status (i.e., primary outcome data) at the end of their scheduled study period.

Protocol Amendments

Any amendments to the study protocol that may affect the conduct of the study or the potential safety of, or benefits to, participants (e.g., changes to the study objectives, study design, sample size, or study procedures) will require a formal amendment to the protocol. Any protocol amendments will be approved by the Principal Investigator, the HiREB, local ethics committees and funders (as needed). Participating clinical sites will also be required to submit amendment requests to their local ethics committees to obtain approval for the amendment, and to provide the Methods Centre with a copy of this approval. Administrative changes (e.g., minor corrections or clarifications that have no effect on the way the study is conducted) will not need to undergo a formal amendment process.

Safety and Adverse Events

Adverse Event Definition

An adverse event (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study.

Serious Adverse Event Definition

Adverse events are classified as serious or non-serious. A serious adverse event (SAE) is any AE that meets at least one of the following criteria:

- Fatal
- Life-threatening
- Requires or prolongs hospital stay
- Results in persistent or significant disability or incapacity
- A congenital anomaly or birth defect
- An important medical event

Unanticipated Problems Resulting in Risk to Participants or Others

Any incident, experience or outcome that meets all the following criteria should be considered an unanticipated problem that results in risk to participants or others:

- Unexpected in nature, severity, or frequency (e.g., not described in study-related documents such as the ethics-approved protocol or Informed Consent Form, etc.);

- Related or possibly related to participation in research (i.e., possibly related means there is reasonable possibility that the incident, experience or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at greater risk of harm (including physical, psychological, economic or social harm).

Unanticipated problems resulting in risk to participants or others encompass more than what one usually thinks of as AEs. 'Problems involving risk' may not necessarily result in harm. For example, misplacing a participant's study records containing identifiable private information introduces the risk of breach of confidentiality. Confidentiality may or may not be breached, but either way this would be a reportable event. Risks to other must also be reported. For example, an unexpected outburst during questionnaire administration by a study participant that put study personnel at risk would be a reportable event.

Clinical Site Reporting

All AEs, SAEs, or unanticipated problems resulting in risk to participants or others are to be reported to the Methods Centre immediately. Participating clinical sites are responsible for reporting AEs and SAEs to the Methods Centre via the Adverse Event Form in the REDCap Cloud EDC system. The original Adverse Event Forms should be kept on file in the relevant participant's file. Significant new information on ongoing SAEs should also be promptly provided to the Methods Centre via the REDCap Cloud EDC system. Unanticipated problems resulting in risk to participants or others are also to be promptly reported to the Methods Centre via telephone or email.

Participating clinical sites are responsible for reporting SAEs and unanticipated problems resulting in risk to participants or others to their local ethics committee (such as an IRB or REB), or a central ethics committee, in accordance with local reporting requirements. Copies of each report and documentation of ethic committee notification and receipt will be kept in the participating clinical site's study file.

Dissemination Policy

Results from the study will be submitted for publication regardless of whether or not there are significant findings. Every attempt will be made to ensure that the amount of time between completion of data collection and release of study findings is minimized. The Methods Centre

546 will also be responsible for reporting required results on clinicaltrials.gov or other applicable
547 clinical trials registry.
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551 ## Acknowledgements
552 Thank you to the Centre for Evidence Based Orthopaedics for assisting in preparing this
553 protocol.
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558 ## References
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