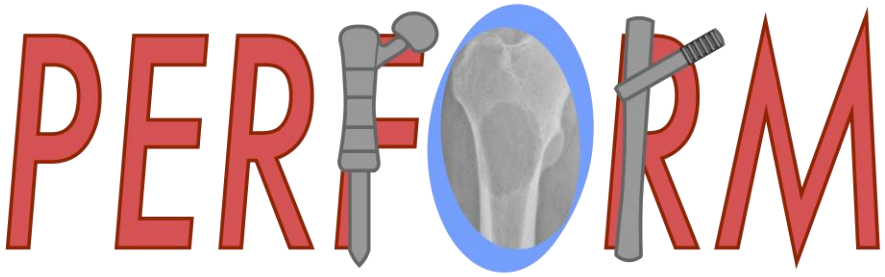

Proximal Femur Reconstruction or Internal Fixation for Metastases

Study Protocol

Version 1.0

This study is registered on ClinicalTrials.gov
Identification No.: XXXX

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List of Abbreviations

AE	Adverse Event
CAC	Central Adjudication Committee
CEAC	Cost-Effectiveness Acceptability Curve
CI	Confidence Interval
CONSORT	Consolidated Standards Of Reporting Trials
CRF	Case Report Form
DAMOCLES	Data Monitoring Committees: Lessons, Ethics, Statistics
DSMB	Data and Safety Monitoring Board
HiREB	Hamilton Integrated Research Ethics Board
ICEMAN	Credibility of Effect Modification Analyses
IRB	Institutional Review Board
LTFU	Loss to Follow-Up
LY	Life Years
PARITY	**P**rophylactic **A**ntibiotic **R**egimens **I**n **T**umor surger**Y** Trial
PERFORM	**P**roximal F**E**mur **R**econstruction or Internal **F**ixation f**OR** **M**etastases Trial
PRECIS-2	Pragmatic-Explanatory Continuum Indicator Summary
PROM	Patient-reported Outcome Measures
PROMIS	Patient-Reported Outcomes Measurement Information System
PROPr	Preference scoring system
QALY	Quality Adjusted Life Years
RCT	Randomized Controlled Trial
REB	Research Ethics Board
SAE	Serious Adverse Event
SAFETY	**S**urveillance **AF**ter **E**xtremity **T**umor surger**Y** Trial

Study Summary

Title	**P**roximal F**E**mur **R**econstruction or Internal **F**ixation f**OR M**etastases Randomized Controlled Trial
Short Title	PERFORM
Methodology	Multi-centre, parallel-arm superiority randomized controlled trial (RCT)
Coordinating Centre	This trial will be centrally coordinated by the Department of Surgery Methods Centre at McMaster University in Hamilton, ON, Canada.
Clinical Sites	20-30 clinical sites across Canada, the United States and internationally.
Primary Objective	The overall objective of the PERFORM trial is to determine the effect of resection and reconstruction on patient-important outcomes compared to internal fixation for the stabilization of an impending or realized pathologic fracture in patients with metastatic bone disease of the proximal femur. We hypothesize that resection and reconstruction will result in improved outcomes as assessed by a hierarchal composite outcome at one year post randomization.
Secondary Objectives	We will assess each component of the hierarchal composite outcome as independent endpoints, as well as the composite outcome at three- and six-months post-surgery. We will also assess the PROMIS-PROPr (PROMIS-Preference) utility score encompassing mental and physical health, and quality of life at baseline, six months, and 12 months.
Treatment Groups	This trial will compare two surgical interventions to stabilize an impending or realized pathologic fracture: 1. Resection and reconstruction with an endoprosthesis or arthroplasty (intervention); or 2. Internal fixation utilizing intramedullary nails, plates and screw fixation +/- tumor curettage (comparator).
Trial Outcome	The definitive primary outcome will be a patient-centered hierarchal composite endpoint consisting of: 1. Mortality at 12 months 2. PROMIS Global Physical Function (patient-reported outcome measure) at 4 months 3. Days at Home at 12 months
Follow-Up	Trial patients will be followed for one-year post-surgery.
Sample Size	334 patients
Estimated Trial Duration	*Trial Initiation:* January – December 2025; *Enrolment*: June 2025 – December 2028; *Follow up:* December 2029
Significance	Due to the rapidly evolving landscape of cancer survivorship, the traditional methods of stabilizing bones in the setting of metastatic bone disease may no longer be meeting the standard of outcomes required for cancer patients who can now live for years with their disease. A growing body of retrospective evidence suggests the advantages of resection and reconstruction over internal fixation for disease control and other cancer-related, surgical, and quality-of-life outcomes, although all current recommendations are based on low-level evidence. The PERFORM trial has the potential to effect significant change in clinical practice and improve the surgical, functional, and quality-of-life outcomes of patients with metastatic bone disease of the proximal femur. However, the introduction of a more invasive, yet more durable, procedure would represent a paradigm shift in the approach to this orthopaedic patient population and, therefore, must be supported by high-quality, concrete evidence.

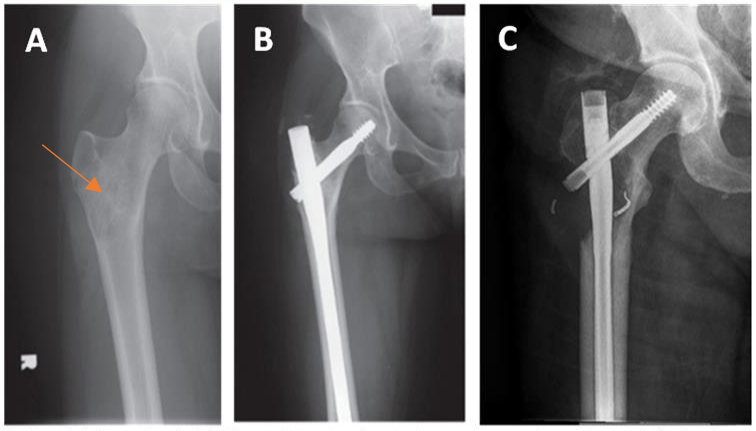
1.0 Introduction

1.1 Burden of Metastatic Bone Disease of the Proximal Femur

Over 16 million individuals are currently living with cancer of any type in North America alone, with the annual incidence estimated at 2 million in 2023.[1,2] Cancer patients are living longer with metastatic disease in almost all cancer types due to improved oncologic control as a result of advancements in cancer therapies.[3] The skeleton is among the most common anatomic locations for metastatic cancer, and the long-term survival of cancer patients with bone metastases has more than tripled in the last quarter of a century.[4] It is estimated that there are over 300,000 individuals presently living with bone metastases in North America.[5] Among cancer patients with bone metastases – or metastatic bone disease (MBD) – the proximal femur represents the most common location in the appendicular skeleton and a source of substantial morbidity.[6]

1.2 Current Surgical Treatment of Skeletal Metastases to the Proximal Femur

The proximal femur is exposed to the highest mechanical forces in the body. While bone-modifying agents and radiotherapy can be used to manage pain, the risk of proximal femur fracture remains high due to cancer induced bone fragility. Prophylactic surgery is the cornerstone of treatment to protect the mechanical integrity and stability of the bone. While surgical treatment is unlikely to increase life expectancy, surgical stabilization can improve the quality of the patient's remaining life by relieving pain and maintaining or regaining function. The traditional surgical approach for MBD in the proximal femur is the stabilization of the pathologic bone with internal fixation (**Figure 1**). The advantages of internal fixation include its simplicity, low morbidity, and relatively low cost.[4] Retrospective data also suggests a low rate of surgical site infections following internal fixation, likely due to the minimally invasive nature of the procedure. However, disease recurrence after internal fixation is becoming increasingly common and can result in devastating implant failures; deleterious effects on function, mobility, and quality of life; and a subsequent need for revision surgery.[7]

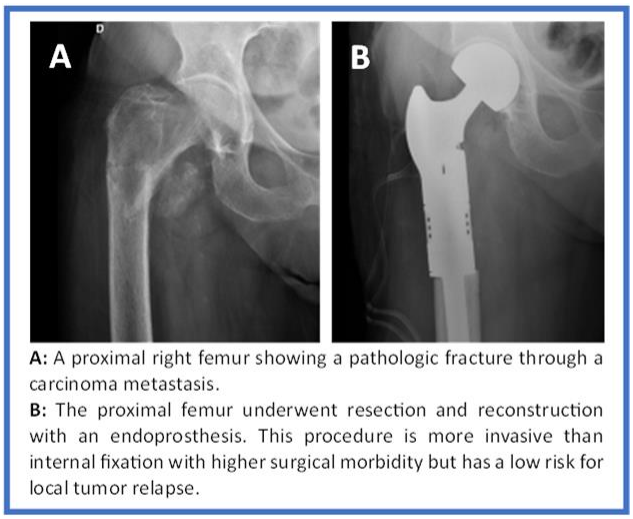


A: A painful proximal right femur intertrochanteric carcinoma deposit at risk for fracture (red arrow).
B: Internal fixation of the lesion with an intramedullary nail. This procedure is minimally invasive with relative low morbidity.
C: Disease progression of carcinoma can lead to pain, immobility, lack of fixation and implant failure.

Figure 1. Internal Fixation

1.2.1 Rationale for Resection and Reconstruction

Alternatively, resection and reconstruction with an endoprosthesis is an orthopaedic surgical technique gaining in popularity for MBD of the proximal femur (**Figure 2**).[8] The advantages of resection with endoprosthetic reconstruction include the immediate stability of the bone without the need for bone healing; and the removal of all local disease during the procedure, reducing the risk for local disease relapse and the need for post-operative local radiotherapy.[4,6] The available evidence, provided by retrospective comparative studies, has found that revision rates due to disease relapse may be up to three times lower with resection and reconstruction than with internal fixation.[7,9–12] Therefore, resection and reconstruction may avoid the harmful effects on function, mobility and quality of life that result from implant failure and revision surgeries. A recent systematic review of retrospective data highlighted the relative durability of resection and reconstruction, an important consideration in a population with increasing life expectancies.[13] However, given the complexity and duration of these procedures, they are costly and patients are at a higher risk of peri-operative complications, such as hip dislocation and surgical site infection.[4]



A: A proximal right femur showing a pathologic fracture through a carcinoma metastasis.
B: The proximal femur underwent resection and reconstruction with an endoprosthesis. This procedure is more invasive than internal fixation with higher surgical morbidity but has a low risk for local tumor relapse.

Figure 2. Resection and Endoprosthetic Reconstruction

1.3 The Need for the Trial

Due to the rapidly evolving landscape of cancer survivorship, the traditional methods of stabilizing bones in the setting of MBD may no longer be meeting the standard of outcomes required for patients who often live for years with their disease. A growing body of retrospective evidence suggests the advantages of resection and reconstruction over internal fixation for disease control and other cancer-related, surgical and quality-of-life outcomes. However, all current recommendations are based on low-level evidence.[14]

Moreover, we recently conducted a modified Delphi study to develop a consensus-based research agenda. From this process that included 80 delegates consisting of orthopaedic oncologists and patients from 18 countries, we identified the most feasible and important research questions to enhance patient care.[15] The evaluation of surgical options for MBD ranked in the top three research questions out of a preliminary list of nearly 200.[15,16]

1.4 Stakeholder Engagement and Collaboration

We have pioneered a patient-engagement paradigm in prospective orthopaedic oncology clinical research that has included patient and caregiver engagement throughout the research continuum and adheres to the ten-step Comparative Effectiveness Research/Patient-Centered Outcomes Research Framework for Continuous Patient Engagement.[17] In the Surveillance AFter Extremity Tumor surgerY (SAFETY) trial, we partnered with sarcoma patients from the onset of the trial's development to ensure that their perspectives were reflected in all stages including the identification of the research question itself. We have continued this paradigm in the PERFORM trial through the engagement of advanced cancer patients and caregivers in the research question development, trial design and the identification and ranking of outcomes that are important to them.

Our research consortium published the Prophylactic Antibiotic Regimens In Tumor surgerY (PARITY) international randomized controlled trial, which demonstrated, *for the first time*, that despite the challenges associated with prospective clinical research in small sub-specialties like orthopaedic oncology, investigator-initiated clinical trials in this field are indeed possible with international collaboration.[18] Through our conduct of both the PARITY and SAFETY trials, our consortium has grown to over 60 clinical sites across Canada, the United States, Argentina, Australia, Austria, Belgium, Brazil, Egypt, Germany, India, Italy, Malaysia, the Netherlands, Portugal, Singapore, South Africa, Spain, Sweden, and the United Kingdom.

1.5 Evidence for Current Practice

A comprehensive clinical practice guideline on the management of MBD of the femur,[14] which required an exhaustive systematic review of the available evidence, concluded that: 1) failures due to local disease relapse are increasingly common after internal fixation for MBD of the proximal femur; 2) there are potentially lower risks of re-operation due to disease relapse with resection and reconstruction; and 3) a clinical zone of equipoise can be identified in which surgeons are comfortable with both procedures.[9,10,19–22] This data guided baseline risk estimates, expected treatment effect and eligibility criteria for the PERFORM trial. Through collaboration with the International MBD Registry, we have determined that: 1) the intertrochanteric and subtrochanteric regions of the proximal femur are the most common locations for surgical MBD in the proximal femur; 2) resection and endoprosthetic reconstruction is increasingly being used in these cases; and 3) the remaining cases were managed with arthroplasty and either intramedullary nailing, plating or curettage. It is important to note that the available evidence does not provide meaningful information on patient-reported outcomes in MBD of the proximal femur. Therefore, the PERFORM trial will also make important progress in the improvement of patient-centered care for this surgical population.

1.6 Clinical Equipoise

1.6.1 Patient Population of Clinical Equipoise

The target population for the PERFORM trial will be any adult person with MBD of the proximal femur in the intertrochanteric and/or subtrochanteric regions with an impending or realized pathologic fracture. The practical application of a protocol that reliably defines and identifies this population in the zone of clinical equipoise has been further discussed through multiple investigator meetings and a cross-sectional survey of the field.

1.6.2 Zone of Clinical Equipoise

The size and extent of metastatic lesions in the intertrochanteric and/or subtrochanteric regions of the femur may dictate if a lesion is ‘too advanced’ for which internal fixation would not provide sufficient stability. Previous work in Japan has suggested that transverse destruction greater than 50% of the width of the bone and/or soft-tissue involvement dictate the use of an endoprosthesis over internal fixation.[19] Our survey work and investigator meeting discussion has resulted in a zone of equipoise of no more than 75% bone destruction and no less than 25% bone destruction.[23] The presence of a pathologic fracture versus an impending fracture may result in a differential treatment effect in the internal fixation group, as the proximal femur in these cases is inherently less stable. Therefore, we plan to stratify randomization based on this variable.

1.6.3 Life Expectancy of Target Population

Our previous work, the survey results, and stakeholder discussions have indicated that a life expectancy of at least six months would be reasonable for clinicians to consider both surgical options. [19,23] Since life expectancy will be based on an estimated clinical judgement, clinicians have expressed that they feel comfortable with this timeline. In addition, functional outcomes and early oncologic events are best assessed within 4-6 months post-operatively, as functional improvements tend to reach a stable threshold at this time in this patient population.[24]

1.7 Most Relevant Patient-Reported Outcome Measures (PROMs)

When selecting PROMs for the PERFORM trial, it was important to consider the outcomes that are most relevant to the patient population being evaluated. We have conducted a virtual focus group with eight members of our patient and caregiver advisory group to facilitate the selection of the most relevant and patient-focused PROMs. Focus group participants included advanced cancer patients with metastatic disease and caregivers of this patient population who had diverse backgrounds and experiences. The arising discussion was confidential and moderated by one of our collaborators specializing in PROMs methodology to ensure that all participants were

able to safely share their perspectives. The discussion was recorded and transcribed for thematic analysis. The main themes from the focus group that emerged were: the impact of treatment on their daily life, being independent and living a normal life, and the impact of the cancer treatment on their quality of life. Based on the analysis of the focus group and the literature, it was determined that the most important outcomes for the PERFORM trial would be the following, and these were later ranked based on further work with clinicians and patient representatives (see **Section 1.8** below):

- Mortality within 12 months
- Days at home within 12 months
- Physical function as assessed by a PROM at 4 months

1.8 Hierarchal Composite Outcome

The utilization of hierarchal composite endpoints provides benefits for both statistical and clinical interpretation as it helps to establish a ranking system among individual outcomes within the composite, thereby addressing concerns regarding endpoint equivalence that can arise with traditional composites. Dr. Nathan O'Hara is an expert in research methodology and has led our team in the use of behavioral economic techniques to identify patient preferences for outcomes.[33-35] To achieve this, we have virtually conducted a discrete choice experiment as part of our stakeholder engagement framework to quantify the outcome priorities of the target population. This process involved individual stakeholders being presented with hypothetical comparisons of different outcomes after surgical management of MBD of the proximal femur, such as a minimum clinically important difference in a PROM, disease relapse requiring re-operation, re-operations for other indications, or mortality. By pooling responses from our sample of 86 stakeholders for this planning step, we have determined the relative importance of the various outcomes and the minimum significant differences that patients desire that would allow them to choose the more invasive surgery.

Please refer to **3.2 Outcome Measures** for the results of the discrete choice experiment to determine the hierarchal composite outcome.

1.9 Summary of Background and Rationale

The population of those living with MBD of the proximal femur is growing precipitously due to the changing landscape of cancer survivorship. The traditional methods of stabilizing bones in the setting of MBD may no longer be meeting the standard of outcomes required for patients who can now live for years with their disease and are at risk of outliving their femoral hardware. A growing body of retrospective evidence suggests the advantages of resection and reconstruction over internal fixation for disease control and other cancer-related and surgical outcomes. As such, there is an increasing need to understand the best surgical approach to MBD of the proximal femur.

2.0 Study Objectives

2.1 Research Objectives

2.1.1 Primary Research Objective

The primary objective of the PERFORM trial is to determine if resection and reconstruction improves patient-important outcomes compared to internal fixation for patients with MBD of the proximal femur. *We hypothesize that resection and reconstruction will result in greater improvements as assessed by a hierarchal composite outcome at 1 year*.

2.1.2 Secondary Research Objective

We will assess the individual components of the composite outcome as independent endpoints, as well as the composite outcome at three- and six-months post-surgery as secondary outcomes. We will also assess the

PROMIS-PROPr (PROMIS-Preference) utility score - encompassing mental and physical health, and quality of life at baseline, six months, and 12 months.

2.2 Subgroup Objectives

We will explore two clinically relevant subgroups based on life expectancy at baseline and fracture status. Life expectancy will be dichotomized as life expectancy greater than one year versus less than one year, and fracture status will be classified as either impending fracture or pathologic fracture. *We hypothesize that patients with a longer life expectancy and those with an impending fracture prior to surgery will have greater treatment benefits from the more invasive surgical procedure.*

3.0 Study Design

The PERFORM trial will be a multi-centre, parallel two-arm superiority randomized controlled trial of patients with MBD of the proximal femur who require surgical management of an impending or realized pathologic fracture. Participants will be randomized in a 1:1 manner to undergo surgical management with either resection and reconstruction or internal fixation. Details on the surgical procedures are provided in **4.5 Study Interventions** below.

3.1 Pragmatic-Explanatory Continuum

Based on the Pragmatic-Explanatory Continuum Indicator Summary (PRECIS-2) toolkit, the PERFORM trial design favors a highly pragmatic approach, and the trial is designed to determine if the interventions work under usual conditions, as opposed to under ideal conditions. The PRECIS-2 tool uses a five-point Likert scale in nine domains to evaluate the continuum of design choices where a score of five is 'very pragmatic,' while a score of one suggests 'very explanatory.' The PERFORM trial design scores either four or five in all domains (**Table 1**).

Table 1. PERFORM Trial PRECIS-2 Score

Domain	Score	Rationale
Eligibility *Who is selected to participate in the trial?*	4	The eligibility criteria are broad and include most patients with MBD of the proximal femur.
Recruitment *How are participants recruited into the trial?*	5	All eligible patients treated at each participating clinical site will be approached to participate during their pre-operative appointment/assessment when surgical management options are discussed. However, trial consent will ideally not be obtained until closer to the start of surgery (and immediately prior to randomization). This decision follows the principle of obtaining consent and enrolling patients as late as possible prior to the start of the intervention in order to avoid missing eligible patients, as well as to avoid the inclusion of ineligible patients.
Setting *Where is the trial being conducted?*	4	Recruitment will take place at multiple sites in Canada, the United States, and internationally. However, although both surgical procedures are standard practice for all orthopaedic oncology surgeons, some surgeons may not have equal experience with both procedures. To mitigate the risk of either selection or performance bias, only clinical sites that demonstrate equivalent expertise availability will be invited to participate. Therefore, although MBD can be treated at either secondary or tertiary care centres, it is likely that only tertiary care centres will be involved in the trial.
Organization *What expertise and resources are needed to deliver the intervention?*	4	The interventions may require some adjustments to clinical care delivery (particularly with respect to surgeon expertise), but it will not require any increase in care providers. A trial conduct training session will be provided to all participating clinical sites before they begin enrolment.
Flexibility (Delivery) *How should the intervention be delivered?*	5	The interventions will be delivered in a manner consistent with standard practice. The Methods Centre is not dictating the specifics of the surgical implants, as different centres have different implants available.
Flexibility (Adherence) *What measures are in place to make sure participants adhere to the intervention?*	4	Both surgical interventions fall within the spectrum of accepted practice. The trial consent process will take place after eligibility is confirmed and immediately prior to surgery to prevent unplanned conversions between the trial arms and withdrawals of consent immediately prior to surgery.
Follow-Up *How closely are participants followed-up?*	5	Post-surgical follow-up is an important element of oncologic care. The follow-up schedule aligns with the standard follow-up practice and adheres to all relevant guidelines. Generous visit windows have been developed to accommodate the clinic schedules of investigators and participant availability.
Primary Outcome *How relevant is it to participants?*	5	The components of the primary hierarchal composite outcome have been validated by MBD patients as being both important and relevant. The ranked approach also aligns with clinical practice, as patients and care providers are typically interested in the treatment effect on multiple outcomes with a defined hierarchy. The primary outcome will not require specialized expertise beyond the treating physicians for diagnosis.
Primary Analysis *To what extent are all data included?*	5	All available trial data will be used for analysis following the intention-to-treat principle.

3.2 Outcome Measures

3.2.1 Primary Outcome: Hierarchal Composite Outcome

The primary outcome for the PERFORM trial will be a patient-centered hierarchal composite endpoint, including the four constructs we identified in our stakeholder and patient engagement framework: 1) Mortality as assessed at 12 months, 2) Physical function as assessed at 4 months using the Patient-Reported Outcomes Measurement Information System (PROMIS®) Global Physical Function score, and 3) Number of days at home as determined at 12 months. The data **(Table 2)** below has been extrapolated from the literature and will be hierarchically assessed in the order listed below. The hierarchal order was determined by discrete choice experiment responses from surgeons, caregivers and patient partners (n=86) that allowed for prioritization of the outcomes within the hierarchy.

Table 2. Expected Proportion of Outcomes in the Sample (Stratified by Treatment Arm)

Level	Outcome	Expected Outcomes		
		Overall	Internal Fixation	Resection and Reconstruction
1	Mortality at 12 months	30%	30%	30%
2	PROMIS Global Physical Function (patient-reported outcome measure) * at 4 months	3.5	4.0	3.0
3	Days at Home ** at 12 months	320	300	340

** Higher values = better function, minimal clinically important difference is 0.5. 'To what extent are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries or moving a chair?' (Range 5: completely to, 1: not at all).*

** Days with no interaction with the healthcare system, patient diary reported

3.2.2 Secondary Outcomes

We will also assess each component listed in **Table 2** above as independent endpoints and the composite outcome at three- and six-months post-surgery as secondary outcomes. Another key secondary outcome will be the PROMIS-PROPr (PROMIS-Preference) utility score - encompassing mental and physical health, quality of life at baseline, six months, and 12 months. This secondary outcome aligns with our patient and caregiver qualitative research themes. The PROMIS-PROPr combines scores from seven PROMIS domains into a single preference-based score (also called a health utility score), which captures the preferences of the general adult population. The total number of items that the patient answers are 31. This instrument gives four different scores: health utility score, domain level scores (one for each of the following domains: physical function, anxiety, depression, fatigue, sleep disturbance, social roles and activities, pain interference, cognition, and pain intensity), physical component score, and a mental component score.

4.0 Study Methods and Procedures

4.1 Study Setting

Under the leadership of the Principal Investigator, our trial team within the Department of Surgery Methods Centre at McMaster University will centrally manage the PERFORM trial. For the definitive trial, we intend to recruit patients from approximately 20-30 clinical sites across Canada and the United States, as well as select international sites with whom we have a history of productive collaboration. Clinical sites will be carefully screened prior to receiving an offer to participate in the trial. The clinical site inclusion criteria will be: 1) adequate research personnel and infrastructure to manage the trial; 2) sufficiently high MBD volume to complete enrolment within the trial timeline (defined as greater than or equal to 12 eligible patients per year); 3) commitment from all or most of the site's orthopaedic oncologists to participate in the trial and that they are comfortable with randomizing all eligible patients (i.e. no potential bias); and 4) access to the required equipment for the two

surgical procedures. The exclusion criteria are: 1) lack of interest in the trial; 2) anticipated challenges with complying with the protocol; 3) conflicting studies that would inhibit patient participation; 4) financial or contractual constraints; and 5) exceptionally poor performance in the PARITY and/or SAFETY trial(s), if applicable. We will remain mindful of the geographic location and expected participant demographics of each clinical site to ensure that the trial sample is geographically and demographically diverse, and that it adequately reflects the spectrum of patients with MBD.

4.2 Trial Population

Extensive background work has established a zone of equipoise in which surgeons would consider both surgical approaches (reconstruction or internal fixation) to be equally appropriate. This background work included a survey of the field[23] and three investigator meetings. The zone of equipoise, therefore, provides inclusion and exclusion criteria that are acceptable to the field (**Table 4**). All patients 18 years of age or older who present with MBD of the proximal femur and who require surgery will be screened. Patients with Multiple Myeloma and Lymphoma will also be screened and included, if eligible.

Table 4: Inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
Life expectancy of at least 6 months	Lesions isolated to the femoral neck
Lesions in the proximal femur (femoral neck, intertrochanteric region, subtrochanteric region, and combinations thereof)	Lesion with any femoral head involvement
Low or intermediate risk for perioperative morbidity and/or mortality	High risk for perioperative morbidity and/or mortality
No more than 75% and no less than 25% bone loss	Multidisciplinary decision that resection of the entire lesion would be indicated
Mutual (patient and physician) decision to perform surgical management of an impending or realized pathologic fracture due to MBD of the proximal has been made.	

4.3 Recruitment and Informed Consent

Ethics approval will be obtained at the Methods Centre and at each clinical site before recruitment begins. Each participating clinical site's locally responsible investigator will oversee the administration of the trial at the site level. To screen MBD patients for eligibility, the locally responsible investigator, along with designated personnel, will develop a site-specific patient enrolment plan. Typically, this plan will include participation in patient rounds and a review of weekly clinic schedules for patients with MBD of the proximal femur. While the management of MBD patients can vary between sites, patients will typically become eligible and will be screened once the surgical management options have been discussed with the patient. The sequence of care a MBD patient typically undertakes is outlined in **Figure 3** below.

The initial introduction of the trial to patients will take place after the discussion of surgical management options has occurred. At this time, patients will be provided with the participant information sheet and informed consent form. Given the surgical nature of the trial interventions, consent to participate in the trial must occur prior to the start of surgery. Therefore, to facilitate an improved consent process that prevents undue decision-making stress for patients awaiting surgery for their impending or realized pathologic fractures, the consent process will, when possible, take place at a later time either on the local inpatient ward (if the patient was admitted from the outpatient clinic or emergency room) or via telephone/email (if the patient was discharged and is to return to the hospital at a later date for surgery). This decision also follows the principle of obtaining consent and enrolling patients as late as possible prior to the start of the intervention to avoid missing eligible patients, as well as to avoid the inclusion of ineligible patients.

Trial personnel at each clinical site will obtain informed consent from patients prior to randomization. Either electronic, written, or verbal consent via telephone may be obtained, as approved by the local ethics committee. If a patient is unable to provide informed consent (e.g., language restriction or due to their disease), informed consent will be obtained from their proxy, if available. If a patient leaves clinic prior to being invited to participate in the trial, the local trial personnel site may obtain verbal consent via telephone or electronic consent via email, as per local ethics committee approval. Upon providing informed consent, participants will be followed in the trial for one year. However, they may withdraw their consent at any time.

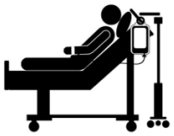
The process of obtaining and documenting informed consent will be completed in accordance with local Good Clinical Practice recommendations. Consent procedures will comply with the appropriate ethics committee and any applicable regulations. At minimum, the following process will be observed by delegated personnel to obtain informed consent:

- Present trial information in a manner that is understandable to the potential trial patient/proxy;
- Discuss the trial with the potential trial patient/proxy and answer any questions they ask;
- Allow the potential trial patient/proxy an opportunity to discuss participation with others, if desired;
- Confirm that the potential trial patient/proxy understands the risks and benefits of participating in the trial and that their participation is voluntary;
- Complete and obtain the appropriate signatures on the approved Informed Consent Form and collect contact information from the trial patient/proxy; and
- Provide the trial patient/proxy with a copy (paper or electronic) of the signed Informed Consent Form.

Trial personnel at clinical sites will be trained to approach any and all potentially eligible patients (should they agree to be approached). They will receive ongoing training at annual Investigators Meetings and monitoring visits, with guidance from our patient partners and trial team.

Figure 3. Typical Sequence of Care of MBD Patients

		Key Personnel	Interventions
Detect Bone Pain or Break		Patient	Self-assessment
Discuss with Medical Oncologist or Emergency Room Physician		Physician, Nurse, Physician Assistant	Medical assessment, imaging, blood tests
Refer to Orthopaedic Oncology Surgeon		Surgeon, Nurse, Radiologist	Medical assessment
Diagnosis and Staging		Surgeon, Nurse, Radiologist	Imaging, biopsy
Trial Intervention: Surgery			

Resection and Endoprosthetic Reconstruction OR Internal Fixation			
Surgery		Surgeon, Nurse, Anesthetist, Medical Oncologist, Radiation Oncologist	Tumor excision or fixation, anesthetic, antibiotics
Post-Surgical Recovery		Surgeon, Nurse, Anesthetist	Pain medication, antibiotics, monitoring
Discharge		Family, Friends	Pain medication, wound care
Rehabilitation		Family, Friends, Physical Therapist, Occupational Therapist, Wound Care Clinics/Nurses	Physical therapy
Full Recovery		Yes 	Patient discharged from Orthopaedic Oncology surgeon's care
		No 	**OUTCOME:** Death, limited physical function, many days in hospital, and/or local cancer recurrence

4.4 Randomization

After providing informed consent, participants will be randomized in a 1:1 ratio to receive either resection and reconstruction or internal fixation. A centralized web-based randomization system (www.randomize.net) will be used to ensure the concealed allocation of participants. Treatment allocation will be determined using random variable block sizes to avoid a substantial imbalance in the number of participants assigned to each treatment group. To ensure balance across groups for any key prognostic and treatment-related variables, such as regional differences in MBD management, the randomization process will be stratified by: 1) impending or pathologic fracture, and 2) clinical site.

4.5 Study Interventions

4.5.1 Internal Fixation

If the participant is randomized to the Internal Fixation treatment arm, the surgery will involve the stabilization of the remaining bone with either an intramedullary nail, plate or screw fixation. All standard surgical principles of stable internal fixation will be followed. The type of fixation, the surgical approach, and the intra-operative use of cement and other adjuvants for disease control will be at the treating surgeon's discretion. We will, however, record these surgical details on the trial CRFs.

4.5.2 Resection and Reconstruction

If a participant is randomized to the Resection and Reconstruction treatment arm, a proximal femoral resection or hip arthroplasty will be carried out as per standard surgical practice. The type of endoprosthesis used for reconstruction will be at the treating surgeon's discretion. Acetabular reconstruction (if any), the surgical

approach, and the intra-operative use of cement and other adjuvants for disease control will also be at the discretion of the treating surgeon. We will, however, record these surgical details on the trial CRFs.

4.5.3 Standardization of Perioperative Care

The random assignment will only specify the type of surgical procedure. To ensure that differences in pre-, peri- and post-operative regimens across clinical sites do not impact trial outcomes, the following key aspects will be standardized. Pre-operatively, prophylactic antibiotics will be administered within one hour of the start of the procedure, with the specific antibiotic at the discretion of the treating surgeon. Post-operatively, antibiotics will continue for 24 hours with the specific choice of antibiotic and regimen at the discretion of the treating surgeon. Thromboprophylaxis will be prescribed, with the specific agent at the discretion of the treating surgeon. All participants will be mobilized within 24 hours of surgery; weightbearing will be advanced as per the treating surgeon's best judgment. The type of anesthesia will be left at the discretion of the local care team. Due to a lack of evidence favoring a particular approach, we will not standardize the use of post-operative hip precautions, physiotherapy/rehabilitation programs and pain management – rather, they will be left at the discretion of the treating surgeon. We will, however, record details of all these variables on the trial CRFs.

4.6 Data Collection and Participant Follow-Up

At baseline, we will collect pre-operative demographic and cancer-related data from various sources, including the participant or proxy, the participant's medical chart, and/or the participant's treating surgeon. The data will include details such as age, sex and gender, co-morbidities, life-expectancy based on surgeon estimate and pre-surgical functional status, and anatomic characteristics of the femoral metastatic lesion. Participants will also pre-operatively complete the PROM questionnaires. We will document surgical details, peri-operative care, and in-hospital data, including the timing of surgery and any co-interventions used that may mediate treatment effects (such as post-operative mobilization and therapy), as well as any serious adverse events (SAEs) that occurred during hospitalization. After discharge, participants will be followed for one year, during which they will be assessed by their treating surgeon at two and six weeks; four, six and nine months; and one-year post-surgery. At each visit, we will document physical therapy, ability to ambulate, re-operations, hospitalizations, and SAEs. PROM data will be collected at all visits; however, the burden is low due to the short nature of the questionnaire. The utility score from the PROPr: PROMIS®-Preference Scoring System will be collected at baseline and 6 and 12 months. Trial data will be securely stored in the trial database accessible only to authorized personnel. See **Table 4** below:

Table 4. Study Flow

CATEGORY	STEPS		DATA COLLECTED
Recruitment	Identification of Patients		
	Assessment of Patient Eligibility		Screening Data
	Informed Consent		Informed Consent Form
Pre-Operative (Baseline)	Pre-Operative (Baseline) **RANDOMIZATION**		Demographics Cancer-related data **PROMIS®-PROPr questionnaire** PROMIS® Physical Function
	Internal Fixation	**Resection and Reconstruction**	
Follow Up Visits	Peri-Operative	Peri-Operative	Surgical details Peri-operative care Serious Adverse Events (SAEs)
	2 Week	2 Week	**Follow-Up Data Package:** X-rays; PROMIS® Physical Function questionnaire; Demographics, health-related questions, Mortality Status; Patient-reported days at home; Recurrence of cancer; SAEs
	6 Week	6 Week	**Follow-Up Data Package**: X-rays; PROMIS® Physical Function questionnaire; Demographics, health-related questions, Mortality Status; Patient-reported days at home; Recurrence of cancer; SAEs
	4 Month	4 Month	**Follow-Up Data Package:** X-rays; PROMIS® Physical Function questionnaire; Demographics, health-related questions, Mortality Status; Patient-reported days at home; Recurrence of cancer; SAEs
	6 Month	6 Month	**Follow-Up Data Package:** X-rays; PROMIS® Physical Function questionnaire; Demographics, health-related questions, Mortality Status; Patient-reported days at home; Recurrence of cancer; SAEs **PROMIS®-PROPr questionnaire**
	9 Month	9 Month	**Follow-Up Data Package:** X-rays; PROMIS® Physical Function questionnaire; Demographics, health-related questions, Mortality Status; Patient-reported days at home; Recurrence of cancer; SAEs
	12 Month	12 Month	**Follow-Up Data Package:** X-rays; PROMIS® Physical Function questionnaire; Demographics, health-related questions, Mortality Status; Patient-reported days at home; Recurrence of cancer; SAEs **PROMIS®-PROPr questionnaire**

PROMIS®: Patient-Reported Outcomes Measurement Information System; PROPr: PROMIS®-Preference Scoring System

4.6.1 Maximization of Follow-Up

Post-surgical follow-up is an important element of oncologic care. Therefore, given that our trial follow-up visits align with the standard follow-up practice, we anticipate only minimal losses to follow-up in our MBD population. Nonetheless, the importance of trial compliance both at the beginning of the trial and at each trial visit will be explained to participants. The following procedures will be implemented to minimize losses:

- Any otherwise eligible patient who is likely to present problems with maintaining follow-up will be excluded;
- At the time of randomization, each participant will be asked to provide their contact information, as well as the contact information for their family physician and three alternate contacts;
- If a participant refuses to return for an assessment, they will be asked if they are willing to provide follow-up data via telephone;
- If a participant cannot be reached, their status regarding the primary trial outcome will be assessed by reviewing their medical chart; and
- Trial personnel will remind participants via telephone/email of upcoming clinic visits.

4.7 Protecting Against Sources of Bias

Our pragmatic trial design carefully balances the internal validity of our eventual results and their generalizability to MBD patients beyond our participating clinical sites. We have carefully considered sources of possible bias and safeguards that we might put in place. To ensure internal validity, we will leverage the experience and advanced clinical trial infrastructure of our trial team. These include procedures for maximizing recruitment, maintaining follow-up, ensuring protocol adherence, and the central adjudication of outcomes, which are detailed in the sections below. When possible, we will blind outcomes assessors and data analysts. Bias could intrude through co-intervention, in particular, differential peri-operative management. We will, therefore, mandate a specific peri-operative management protocol (see 4.5.3 Standardization of Perioperative Care). The generalizability of our results is supported by the diversity of our participating hospitals, the screening of all MBD patients, and the surgical procedures used daily for MBD across North America and worldwide.

4.7.1 Data Monitoring

In addition to our strategies to maximize participant retention, we will also implement a Data Monitoring Plan to prevent missing data and protect the integrity of the data quality. Ongoing remote data monitoring will be conducted by our trial team. Specifically, we will monitor the trial database for missing data, inconsistent or implausible data, enrolment rates, the distribution of key data points (e.g., life-expectancy based on surgeon estimate, pre-surgical functional status, and anatomic characteristics of the lesion), follow-up rates, the number and type of outcomes (e.g., lower than anticipated trial events), and protocol deviations reported by each clinical site. Findings from the remote data monitoring will be distributed to the Principal Investigator, as well as to the site investigator and personnel at the respective clinical site. Our trial team will work collaboratively with the clinical site personnel and site investigators to resolve all identified issues, which may necessitate an ad hoc in-person monitoring visit.

If an in-person site monitoring visit is required, items that will be reviewed at each monitoring visit will include: trial master files, trial procedures, screening data and data verification of 20% of the enrolled trial patients, which will be increased if significant issues are identified. Our trial team will also carefully monitor participants' records to ensure that they received the correct interventions. Findings from each monitoring visit will be recorded and distributed to the trial Principal Investigator, as well as to the investigator and personnel at the respective clinical site. Our trial team will work collaboratively with the clinical site personnel and site investigators to resolve all identified issues. Re-training of clinical site personnel will be provided as necessary.

We achieved a 95% follow-up rate in our PARITY trial in which patients with MBD of the femur were included. Since all MBD patients who have undergone surgical management for an impending or realized pathologic fracture require post-surgical follow-up, we anticipate a similar loss to follow-up (LTFU) rate in the PERFORM trial. As in our previous trials, patients will only be withdrawn if they no longer consent to participate or if clinical site personnel are unable to contact them after several attempts for their one-year follow-up visit. Over the course of the trial, clinical site personnel will receive frequent quality control reports generated by the Methods Centre personnel who will summarize missing or overdue data. Our trial team will follow-up regarding these reports, as well as inform the Principal Investigator who may escalate them to the site investigator to develop a plan to submit the overdue data. If necessary, we will conduct in-person monitoring visits to collect any missing or overdue data points.

4.7.2 Adjudication of Outcomes

The use of Central Adjudication Committees (CAC) in randomized controlled trials significantly increases data quality and reduces inaccuracies by minimizing biased outcome assessment and between-site variability. The membership and responsibilities of the PERFORM CAC will be detailed in the PERFORM CAC Charter. Briefly, the PERFORM CAC will be comprised of three orthopaedic oncologists, a medical oncologist and a radiation oncologist. Using pre-defined decision rules that will be documented in the PERFORM CAC Charter, the PERFORM CAC will adjudicate: 1) case eligibility; 2) unplanned re-operations; 3) local recurrence; 4) serious adverse events and 5) mortality (cause of death). The CAC will reach a consensus on all reviewed cases. All decisions made by the Committee will be final. We anticipate that the PERFORM CAC will meet quarterly to review trial events that require adjudication.

4.7.3 Allocation Concealment and Blinding

The participants, local trial personnel and our trial team cannot be blinded to the surgical procedure, given the differences in surgical incisions for the procedures and the surgeon's need to know which procedure to perform. However, the use of random variable block sizes will minimize the risk of selection bias. Given the obvious differences in hardware utilized between the two surgical procedures, it will also be impossible to blind outcomes assessors when adjudicating events that require the review of imaging. However, for events that do not require the review of imaging, outcomes assessors will be blinded. Finally, safety data reported to the PERFORM Data and Safety Monitoring Board (DSMB) will be compiled by a blinded data analyst who is otherwise not involved in the trial to ensure that the PERFORM data analyst remains blinded.

4.7.4 Minimization of Crossovers of Trial Interventions

Unplanned conversions between the two surgical procedures are unlikely, as only patients who are suitable for both surgical procedures will be eligible for the trial. The likelihood of crossovers is further reduced due to the requirement that the surgical equipment for both procedures be available at all participating clinical sites. When possible, local trial personnel will be present in the pre-operative holding area to obtain study consent and during surgery to ensure that the patient undergoes the correct surgical procedure. Nevertheless, any patients who do crossover will be analyzed in the group to which they were originally allocated, maintaining the intention-to-treat approach planned for our analysis.

5.0 Statistical Plan

5.1 Sample Size Determination

The use of hierarchically assessed composite outcomes is becoming more frequent in clinical trials, and it offers several benefits. By utilizing a pre-defined rank, statistical power increases while avoiding concerns of increased type I errors due to multiplicity. This ranked approach also aligns with clinical practice as patients and care providers are typically interested in the treatment effect on multiple outcomes with a defined hierarchy. Detailed simulations were performed to determine the appropriate sample size to adequately power the study. **Table 5** lists the distributional assumptions for each component of the composite outcome by treatment arm. Using 10,000 simulations of these distributions, we determined that 300 patients (150 per group) provided over 90% power to detect superiority with a two-sided alpha of 5% tested with the U-statistic described by Bebu and Lachin [26]. To account for up to 10% attrition, the trial plans to enroll 334 patients.

Table 5 : Input for sample size estimation.

Rank	Outcome	Resection and Reconstruction	Internal Fixation
1	Death within 12 months	30%	30%
2	Physical function (ability to perform everyday activities) by 4 months		
	Unable to do	5%	10%
	With much difficulty	20%	25%
	With some difficulty	40%	40%
	With little difficult	25%	20%
	Without any difficulty	10%	5%
3	Days at home within 365 days, mean (SD)	340 (20)	300 (20)

5.2 Statistical Methods

5.2.1 Analysis Plan Overview

While conducting the analyses, the data analysts will remain blinded to treatment allocation. The analysis and reporting of the trial will follow the CONSORT criteria (www.consort-statement.org). The process of participant enrolment and flow through the study will be summarized using a flow diagram. Participant demographics and baseline outcome variables will be summarized using descriptive statistics reported as mean (standard deviation) or median (interquartile range) for continuous variables depending on the distribution, and count (percent) for categorical variables. All analyses will use the intention-to-treat principle. We do not plan to conduct a formal interim analysis for efficacy, as the trial will not be stopped early for benefit due to the risk of overestimating treatment effects. Secondary analyses will be exploratory with no adjustments for multiple comparisons.

5.2.2 Primary Outcome Analysis

We will hierarchically assess the primary composite outcome using the Win Ratio method. The Win Ratio method is based on the principle that each participant in the clinical trial is compared with every other participant within each stratum in a pairwise manner. All-cause mortality comparisons will be time-to-event and local cancer recurrence will allow for recurrent events using a frailty model. The pairwise comparison proceeds in a hierarchal fashion – for example, starting with mortality, followed by physical function, followed by days at home, and finally by local cancer recurrence when participants cannot be differentiated on an outcome of higher importance. If two paired participants both experienced a local cancer recurrence, we will assume a greater frequency of recurrences to be worse. If two paired participants have the same mortality status or frequency of recurrences, we will assume earlier events are worse. For each pairwise comparison, the treatment groups are assigned a

win, loss, or tie. The Win Ratio is the frequency of a favorable outcome in participants assigned to resection and reconstruction divided by the frequency of a favorable outcome in participants assigned to internal fixation with a 95% CI and corresponding p-value calculated using the methods described by Finkelstein and Schoenfeld.

5.2.3 Secondary Outcomes Analyses

We will analyze all-cause mortality with a Cox proportional hazards model, re-operation for disease relapse and other indications with frailty models to account for recurrence, and patient-reported outcomes using linear regression models.

5.2.3 Subgroup Analyses

We will explore two clinically relevant subgroups based on life expectancy at baseline and fracture status. Life expectancy will be dichotomized as life expectancy of greater than or equal to one year versus less than one year, and fracture status will be classified as either impending fracture or realized pathologic fracture. We hypothesize that participants with a longer life expectancy and those with an impending fracture prior to surgery will have greater treatment benefits from the more invasive surgical procedure. We will stratify our primary model by the subgroup covariate to assess the presence of effect modification. We will assess the credibility of any observed subgroup effects using the Instrument to assess the Credibility of Effect Modification Analyses (ICEMAN) criteria.

5.2.4 Health Economic Analysis

An economic evaluation of this trial will be conducted to compare the one-year costs and outcomes between the two treatment allocations. QALYs will be utilized as the primary outcome, as is recommended in many countries (e.g., Canada, the United Kingdom and the United States)[27–29]. Life years (LYs) will be used as a secondary outcome.

For the base case analysis, Canadian unit costs will be applied to the economic data collected as part of the trial to estimate the direct (e.g., hospitalizations, surgeries) and indirect costs (e.g., productivity losses) associated with the two treatment allocations. QALYs will be derived using the health utility scores from the PROMIS-PROPr questionnaires collected in the trial using an area under the curve. The base case analysis will use the Canadian algorithm to derive the PROMIS-PROPr health utility scores[30]. Multiple cost-effectiveness acceptability curves (CEACs) presenting the probability of each of the treatment allocations to be cost-effective at several willingness-to-pay thresholds (e.g., $50,000 or $100,000 per QALY gained) will be used to summarize uncertainty. Costs and outcomes will be discounted at 1.5% as per the recommendations of the current Canadian guidelines, and results will be presented from both a payer (e.g., Ministry of Health) and a societal perspective[27]. Scenario analyses will be conducted to explore the impact of varying key assumptions on the results (e.g., using unit costs from the United States, discount rate of 3%). The analysis will be conducted and reported according to best practices for economic evaluations of healthcare technologies (e.g., how to deal with missing or censored data)[31,32].

5.2.5 Sensitivity Analyses

Assessment of the sensitivity or robustness of the findings to the key assumptions is essential in clinical trials. The following sensitivity analyses will be performed:

1) Baseline Prognostic Imbalance Analysis: This analysis will assume a baseline prognostic imbalance between the treatment groups. Adjusted analyses, employing Cox regression models, will be utilized to examine and control for the possible influence of patient factors that might be associated with the elements of the hierarchal composite outcome.
2) "*As-Treated*" Analysis: This sensitivity analysis will account for crossovers in the surgical intervention. The actual surgical intervention will be the independent variable.

6.0 Data Collection and Management

The study CRFs are the primary data collection instrument for the study. Participating clinical sites will be provided with the study CRFs prior to the initiation of local enrolment. All data requested on the CRFs must be recorded, and any missing data must be explained.

6.1 Data Transmission

6.1.1 Electronic Data Capture System – Trial Database

We will utilize the REDCap Cloud system as the PERFORM trial database. All data will be stored on the secure server with no data stored locally on the user's computer. Unauthorized access to the system is restricted by means of a firewall and data encryption protection applied to all communications and data transmissions. Regular system maintenance ensures security risks are minimized. The database will store clinical trial data entered by local site personnel from the PERFORM CRFs. Data will be organized according to trial visit. The preliminary visit schedule is as follows (with permissible visit windows if applicable):

- Screening,
- Baseline,
- 2-Week Follow-Up (1 – 3 weeks post-surgery),
- 6-Week Follow-Up (4 – 8 weeks post-surgery),
- 4-Month Follow-Up (3 – 5 months post-surgery),
- 6-Month Follow-Up (5 - 7 months post-surgery),
- 9-Month Follow-Up (8 - 11 months post-surgery), and
- 1-Year Follow-Up (≥ 12 months post-surgery).

6.1.2 Randomization System

The Randomize.Net randomization system requires internet access and can be used on any device that can connect to the internet (e.g., computer, tablet, smartphone). Randomize.Net is a comprehensive randomization service for clinical trials that allows clients to define features and customize them specific to their trial, including stratification, multiple treatments, block sizes, masking and participating clinical site identifiers (in order for the system to generate unique participant identifiers). Online support is available for questions regarding set-up, updates and problems using the system. The database will store the stratification trial data entered by local site personnel, as well as the treatment allocation and unique participant identifier generated by the randomization system.

6.2 Data Integrity

6.2.1 Data Transmission

Study personnel at each participating clinical site will submit the required data, as detailed on the CRFs, to the Methods Center using the RedCap EDC system. Study personnel at each participating clinical site will receive unique login credentials (username and password) for the EDC systems and will be able to view and modify data for participants recruited at their respective clinical site. Study personnel at each participating clinical site will receive a Study Resource Binder, which will include detailed instructions on using the REDCap EDC system.

6.2.2 Data Integrity

The REDCap EDC system uses a variety of mechanisms for checking data at the time of entry including skip logic, range checks and data type checks. Data cleaning procedures will also be performed on a regular basis. Upon receipt of new data, Methods Center personnel will query all missing, implausible, or inconsistent data. Study personnel will be able to review all open queries for their respective clinical site in the system and will be

required to promptly respond. The Study Resource Binder will include detailed instructions on addressing queries in the RedCap EDC system.

6.2.2 Data Preservation and Sharing

Upon the completion of the follow-up period for all trial participants, and only once all data cleaning activities have been completed, designated trial team members will be responsible for the notification to the Data Manager to remove access to the trial database for all local site personnel. Only the Data Manager, Research Manager, Research Assistant and Study Statistician will continue to have access to the trial database and randomization system. Once the data is extracted and primary analyses are completed and published, the trial team members will make the data available upon request to collaborators for secondary analyses.

7.0 Ethical Considerations

This study is to be conducted according to international standards of Good Clinical Practice, applicable government regulations, and institutional research policies and procedures. Both study arms fall within the spectrum of current standard practice, as do the standardized post-operative follow-up visits.

7.1 Research Ethics Approval

This study protocol will be submitted to a properly constituted independent ethics committee (such as a research ethics board [REB] or an institutional review board [IRB]), in agreement with local legal prescriptions, for formal approval of the study conduct. 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. At each participating clinical site, the decision of the appropriate local ethics committee concerning the conduct of the study will be made in writing to the local investigator. A copy of this decision will be provided to the Methods Center prior to the local commencement of this study.

7.2 Informed Consent Form

All patients eligible for this study will be provided with a Participant Information Sheet and Informed Consent Form describing this study and providing sufficient information for patients to make an informed decision about their participation in this study. The Informed Consent Form will comply with the Health Insurance Portability and Accountability Act, if applicable, and will be submitted with the study protocol for formal review and approval by the appropriate ethics committee. The formal consent of a study participant, using the ethics committee-approved Informed Consent Form, must be obtained prior to the subject undergoing any study procedure.

7.3 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 (for paper documents) and/or secure digital files, and accessible only to study personnel;
- All paper and electronic CRFs will be identified only by a coded participant ID number and initials; and
- All study databases will be password-protected.

The communication, transmission and storage of participant 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 will be made to obtain permission to collect at least vital status at the end of their scheduled study period.

7.4 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 Center 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.

7.5 Safety and Adverse Events

7.5.1 Definitions

7.5.1.1 Adverse Event

An adverse event (AE) is any symptom, sign, illness, or experience that develops or worsens in severity during the course of the study or can be related when there is a reasonable possibility that the event might have been caused by study participation.

7.5.1.2 Serious Adverse Event

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

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

7.5.1.3 Unanticipated Problems Resulting in Risk to Participants or Others

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

- Unexpected in nature, severity, or frequency
- 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 others 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.

7.5.2 Clinical Site Reporting

Participating clinical sites are responsible for reporting related AEs and all SAEs (irrespective of the relatedness of the event to the study intervention) to the Methods Center immediately, as well as their local ethics committee in accordance with local reporting requirements. Unanticipated problems resulting in risk to participants or others are also to be promptly reported to the Methods Center and the appropriate ethics committee if required.

7.5.2.1 Notifying the Methods Center

Participating clinical sites are responsible for reporting related AEs and SAEs to the Methods Center via the Adverse Event Form in the REDCap Cloud database. The original Adverse Event Forms will be kept in the relevant participant's file. Significant new information on ongoing SAEs will also be promptly provided to the Methods Center via the REDCap Cloud system. Unanticipated problems resulting in risk to participants or others are also to be promptly reported to the Methods Center via telephone or email. Detailed instructions on reporting related AEs, SAEs or unanticipated problems resulting in risk to participants or others will be provided to study personnel at each participating clinical site in the Study Resource Binder.

7.5.2.2 Notifying the Appropriate Ethics Committee

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 ethics committee notification and receipt will be kept in the participating clinical site's study file.

7.5.3 Participant Safety and Monitoring

7.5.3.1 Participant Risks and Benefits

Both surgical techniques and associated hardware are indicated and approved for use in MBD patients with impending or realized pathologic fractures of the proximal femur, and they are both commonly used across North America in this patient population. The typical risks of surgery, such as bleeding, infection, deep vein thrombosis and neurovascular injury, apply equally to participants irrespective of the trial arm. These are inherent risks within the operative procedures for the treatment of this condition. Additional risks associated with internal fixation include revision surgery as a result of implant failure or disease recurrence. Additional risks associated with resection and endoprosthetic reconstruction include a potential increased risk of a surgical site infection, given the complexity of the procedure and the more invasive nature of the procedure. Our trial's DSMB will closely monitor event reporting and, should a differential risk of benefits be identified, they will consider stopping the trial. As in any trial, there is a potential risk of a breach of confidentiality. However, our trial team has extensive experience in the management of sensitive patient information and all possible precautions will be taken to ensure the security of these data. We will also work with clinical site personnel to ensure confidentiality is upheld at clinical sites.

Studies show that surgical site infections are less common with internal fixation, only a few percent, compared to up to 10 percent with reconstruction, because it is less invasive, meaning it has smaller incisions. However, there is a concern that with this surgery there may an issue with increased likelihood of recurrent disease, up to 15 or 20 percent, compared to almost none with reconstruction. In fact, reconstruction approaches can last longer, which is important as people live longer with metastatic bone disease. However, these surgeries are complicated, may take a bit longer to complete, and can be expensive. They also have a higher chance of complications, like hip dislocations (a few percent) after the surgery.

It is not clear at this time that one surgical technique will provide any benefit over another. However, all participants will receive treatment for their impending or realized pathologic fracture in a manner that is

considered acceptable and within the standard of care. They may also benefit from the additional observation provided, as well as trial personnel communication and patient-reported outcomes questionnaires.

7.5.3.2 Data and Safety Monitoring Board

As per the principles established by the Data Monitoring Committees: Lessons, Ethics, Statistics (DAMOCLES) Study Group charter, we will establish a DSMB prior to the commencement of the feasibility phase of the PERFORM trial to oversee the safety of the trial participants and the overall conduct of the trial. The PERFORM DSMB will consist of members who are independent of the trial, free of conflicts with any of the investigative team, and will include experts in orthopaedic oncology and biostatistics, as well as an independent patient representative. The membership and responsibilities of the PERFORM DSMB will be detailed in the PERFORM DSMB Charter. Briefly, the DSMB will review accumulated safety data (i.e., SAEs) from the trial reports and advise the Principal Investigators and trial team on items related to trial safety. The DSMB is responsible for safeguarding the interests of participants, assessing the safety and efficacy of trial procedures and monitoring the overall conduct of the trial.

8.0 Knowledge Dissemination

The results of the study will be submitted for publication regardless of whether there are significant findings, as well as posted on ClinicalTrials.gov. Every attempt will be made to ensure that the amount of time between completion of data collection and release of study findings is minimized. Knowledge Dissemination will be conducted under the guidance of patient and caregiver advisors and detailed in a separate Knowledge Dissemination Plan.

9.0 Secondary and Sub-Study Manuscripts

We will strongly encourage requests from co-investigators to publish PERFORM secondary and sub-study manuscripts. The Knowledge Dissemination Plan will provide guidelines for the submission of proposals as well as authorship of secondary and sub-study manuscripts.

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