

**Comparing Total Hip Arthroplasty and Hemi-Arthroplasty  
on Secondary Procedures and Quality of Life in Adults With  
Displaced Hip Fractures**

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**Study Protocol**

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# Health

Hip Fracture Evaluation with Alternatives of  
Total Hip Arthroplasty Versus Hemi-Arthroplasty

## **HEALTH Protocol, Version 10.0**

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**Hip Fracture Evaluation with Alternatives of Total Hip  
Arthroplasty versus Hemi-Arthroplasty (HEALTH):**

**A Multi-Centre Randomized Trial Comparing Total Hip Arthroplasty and  
Hemi-Arthroplasty on Secondary Procedures and Quality of Life in Patients with  
Displaced Femoral Neck Fractures**

**Prepared by:**

**Mohit Bhandari and Gordon Guyatt**

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**LIST OF ABBREVIATIONS**

<b>Abbreviation</b>	<b>Explanation</b>
AE	Adverse Event
ASA	American Society for Anesthesiologists
CAC	Central Adjudication Committee
CI	Confidence Interval
DAMOCLES	Data Monitoring Committees: Lessons, Ethics, Statistics Study Group Charter
D/C	Discharge
DMC	Data Monitoring Committee
DVT	Deep Vein Thrombosis
EQ-5D	EuroQol-5D
HA	Hemi-Arthroplasty
HEALTH	Hip Fracture Evaluation with ALternatives of Total Hip Arthroplasty versus Hemi-Arthroplasty
IHFRC	International Hip Fracture Research Collaborative
INR	International Normalized Ratio
IRB	Institutional Review Board
IU	International Units
LMWH	Low Molecular Weight Heparin
MRI	Magnetic Resonance Imaging
PI	Principle Investigator
PO	By Mouth
Pre-op	Pre-operative
Post-op	Post-operative
PD	Protocol Deviation
PTT	Partial Thromboplastin Time
RCT	Randomized Controlled Trial
REB	Research Ethics Board
RR	Relative Risk
RRR	Relative Risk Reduction
SF-12	Short Form-12
SP	Secondary Procedure
SPRINT	Study to Prospectively Evaluate Reamed Intramedullary Nails in Tibial Fractures
TEDS	Thromboembolic Disease Stockings
TUG	Timed Up and Go
THA	Total Hip Arthroplasty
W/D	Withdraw
WOMAC	Western Ontario McMaster Osteoarthritis Index

## STUDY SUMMARY

<b>Title</b>	Hip Fracture Evaluation with Alternatives of Total Hip Arthroplasty versus Hemi-Arthroplasty
<b>Short Title</b>	HEALTH
<b>Objective</b>	Our primary objective is to assess the impact of total hip arthroplasty versus hemi-arthroplasty (i.e., bipolar or modular unipolar) on rates of secondary procedures at 2 years in individuals with displaced femoral neck fractures.
<b>Hypothesis</b>	We hypothesize that total hip arthroplasty will have similar or lower rates of secondary procedures and higher functional outcome scores at 24 months compared with hemi-arthroplasty.
<b>Study Design</b>	We propose a multi-centre, concealed ‘expertise-based’ randomized trial design using minimization to determine patient allocation. Surgeons across North America, Europe, Asia, and Australia will participate. Patients who have sustained a displaced femoral neck fracture will be randomized to one of two surgical interventions. The first surgical intervention involves total hip arthroplasty (i.e., replacement of the femoral head and hip socket). The second surgical intervention involves a hemi-arthroplasty (i.e., replacement of the femoral head only). Each participating site will have on staff surgeons with expertise in both interventions to ensure adherence to the expertise-based design. Study personnel will monitor critical aspects of peri-operative care and rehabilitation. We will assess patients at hospital admission (baseline), 1 week, 10 weeks, 6 months, 9 months, 12 months, 18 months, and 24 months after surgery. Fracture eligibility when in doubt, technical placement of prostheses, secondary procedures, fracture-related complications, and deaths will be independently adjudicated.

## 1. INTRODUCTION

This document is a protocol for a human research study. This is a multi-centre, blinded, randomized control trial to evaluate two alternative approaches (total hip arthroplasty and hemiarthroplasty) for treating displaced femoral neck fractures in elderly patients. Although current opinion among orthopaedic surgeons favours the use of arthroplasty for displaced femoral neck fractures, there is lack of agreement on which type of arthroplasty is optimal. The rationale for this study is driven by: 1) the high incidence and serious consequences of hip fractures; 2) the orthopaedic community's uncertainty about the optimal type of arthroplasty; 3) a feasible and efficient study design; and 4) extensive support for the trial.

### 1.1 Background

Hip fractures occur in 280,000 Americans (over 5,000 per week) and 36,000 Canadians (over 690 per week) annually (Cummings et al, 1990). By the year 2040, the number of people aged 65 or older will increase from 34.8 million to 77.2 million (U.S. Bureau of the Census, 1998). Demographic projections by Statistics Canada indicate that by the year 2041, 1 in 4 Canadians will be over the age of 65 years (Statistics Canada, 1994). The number of hip fractures is likely to exceed 500,000 annually in the United States and 88,000 in Canada over the next 40 years (Johnell et al, 2004; Cooper et al, 1992; Cummings et al, 1990). By the year 2040, the estimated annual health care costs will reach \$9.8 billion in the United States and \$650 million in Canada (Papadimitropoulos et al, 1997).

Hip fractures are associated with a 30% mortality rate at 1 year (Moran et al, 2005) and profound temporary, and sometimes permanent, impairment of independence and quality of life (Jongjit et al, 2003; Wilkins et al, 1999). Worldwide, 4.5 million persons are disabled from hip fractures yearly with an expected increase to 21 million persons living with disability in the next 40 years (Johnell et al, 2004; Cooper et al, 1992; Cummings et al, 1990). Hip fractures account for more hospital days than any other musculoskeletal injury and represent more than two thirds of all hospital days due to fractures (AAOS, 1999). Length of hospital stays in Canada is estimated at 465,000 patient-days annually with a projected increase to 1.8 million days annually by 2040 (Papadimitropoulos et al, 1997). The disability adjusted life-years lost as a result of hip fractures ranks in the top 10 of all cause disability globally (Cooper et al, 1992).

Hip Fractures are anatomically classified in relation to the hip capsule as intracapsular fractures (i.e., femoral neck) or extracapsular fractures (i.e., inter-trochanteric and sub-trochanteric) (**Figure 1**). This trial focuses on the management of displaced fractures of the femoral neck.

Femoral neck fractures may be either undisplaced (i.e., very little separation at the fracture site, about one third of femoral neck fractures) or displaced (i.e., greater separation, about two thirds of femoral neck fractures) (**Figure 2**). The most popular classification system, the Garden Classification, identifies undisplaced fractures (i.e., Garden types I and II) and displaced fractures (i.e., Garden types III and IV). Surgeons agree that internal fixation, in which a mechanical implant fixes the two segments of bone together, is the best way to manage undisplaced fractures (Bhandari et al, 2005). For displaced fractures, the choice of internal fixation or arthroplasty (which involves replacing the femoral head, hemiarthroplasty (HA), and

sometimes also the acetabulum, total hip arthroplasty (THA) (**Figures 3a, 3b, 3c, and 3d**) with prostheses) depends on patient characteristics and surgeon preference. This trial focuses on displaced fractures in which patient characteristics and preference lead the attending surgeon to plan arthroplasty as the management approach.

## **1.2 Hemi-Arthroplasty**

Advocates of hemi-arthroplasty make claims of reduced dislocation rates, lower rates of deep vein thrombosis (DVT), shorter operating times, less blood loss, a technically less demanding procedure, and lower costs than total hip arthroplasty (Poignard et al, 2011). Newer implant designs (i.e., bipolar and modular unipolar hemi-arthroplasties) have reduced acetabular erosion (i.e., thinning out of the acetabulum) and the resultant need for a secondary procedure, a problem in earlier unipolar designs (i.e., single femoral head and shaft). Furthermore, recent evidence has refuted a prior claim of advantages of bipolar over unipolar hemi-arthroplasties (Raia et al, 2003; Ong et al, 2002; Davison et al, 2001; Cornell et al, 1998). These studies have shown no differences in blood loss, length of hospital stay, dislocation rates, post-operative pain, recovery of ambulatory status, and activities of daily living or post-operative functional outcome scores. These studies have established that unipolar and bipolar hemi-arthroplasties yield similar outcomes.

## **1.3 Total Hip Arthroplasty**

Surgeons supporting total hip arthroplasty perceive benefits in improving patient function and improving quality of life (Skinner et al, 1989). Advocates claim that modern implants have reduced increased dislocation rates that used to plague total hip arthroplasty, and that arthroplasty rates now approximate hemi-arthroplasty rates.

## **1.4 Surgical Management of Hip Fractures – Uncertainty and Controversy**

The lack of definitive evidence regarding the optimal approach for surgical management has fueled debates at international orthopaedic surgical meetings. A survey of 298 surgeons who were members of the Orthopaedic Trauma Association and European clinics affiliated with AO International (Davos, Switzerland) found that although surgeons agreed that arthroplasty is the preferred option in displaced femoral neck fractures (i.e., Garden IV) in patients aged greater than 60 years, they disagreed upon the optimal form of arthroplasty. In the 60 to 80 year old patient, unipolar arthroplasty, bipolar arthroplasty, and total hip arthroplasty received 32%, 41%, and 17% endorsement, respectively.

## **1.5 Alternative Operative Management Strategies in Femoral Neck Fractures – Direct Comparisons for Randomized Trials**

A comprehensive literature search to identify all studies relevant to the relative merits of hemi-arthroplasty versus total hip arthroplasty for displaced femoral neck fractures identified 4 randomized controlled trials (RCTs) comparing internal fixation, hemi-arthroplasty, and total hip arthroplasty. Of these, 1 trial was an updated publication of an earlier study, and another reported only aggregate results for all arthroplasty. Thus, 2 randomized trials (Ravikumar et al, 2002; Keating et al, 2005) provided sufficient detail for statistical pooling of results. Current

best estimates of treatment effect suggest that total hip arthroplasty reduces hip pain (RRR=0.24, 95% CI: 2%-41%), and may reduce functional limitations (RRR=0.10, 95% CI: 24%-26%), when compared with hemi-arthroplasty. The reduction in pain and improvement in function may come at the cost of an increased risk of hip dislocation (RR=2.95%, 95% CI: 0.40-21.74). Despite the trend toward an increase in hip dislocation, the data (point estimate) show a trend toward decrease in secondary procedure rates with hemi-arthroplasty, although the sparse data is associated with very wide confidence intervals (RRR=0.14, 95% CI: 53%-59%). In addition to the small sample sizes, these trials are limited by lack of concealed randomization in 1 trial (Ravikumar et al, 2002), and a differential expertise bias (Devereaux et al, 2005), as more experienced surgeons usually conducted the total joint arthroplasty than the hemi-arthroplasty (Keating et al, 2005).

### **1.6 Hemi-Arthroplasty versus Total Hip Arthroplasty – Indirect Comparisons from Meta-Analyses**

Two meta-analyses (Lu-Yao et al, 1994; Bhandari et al, 2003) were identified that provided indirect comparisons of total hip arthroplasty and hemi-arthroplasty. Lu-Yao pooled observational studies and randomized trials of total hip arthroplasty (N=746 patients) versus hemi-arthroplasty (N=4,530 patients), and found reductions in the risk of secondary procedures, mortality, wound infection, and hip pain with total hip arthroplasty. Bhandari's meta-analysis restricted to randomized trials (N=662 patients) suggested similar rates of secondary procedures, decreased mortality, decreased infection rates, and large benefits in patient function with total hip arthroplasty. Both meta-analyses reported at least 2-fold higher hip dislocation rates with total hip arthroplasty.

In summary, both direct and indirect evidence suggests substantial benefit of total hip arthroplasty over hemi-arthroplasty in decreased pain and improved function. Both direct and indirect evidence suggest increased rates of dislocation with total hip arthroplasty. Despite this increased dislocation rate, indirect evidence suggests similar secondary procedure and mortality rates with the 2 procedures. While direct evidence is consistent with similar rates of secondary procedures and mortality, the data from direct comparisons are so sparse as to be uninformative.

## **2. STUDY OBJECTIVES**

### **2.1 Primary Objective**

The primary objective is to assess the impact of total hip arthroplasty versus hemi-arthroplasty (i.e., bipolar or modular unipolar) on rates of secondary procedures at 2 years in individuals with displaced femoral neck fractures.

### **2.2 Secondary Objectives**

Secondary objectives are:

1. To examine the effect of total hip arthroplasty versus hemi-arthroplasty on health-related quality of life (Short Form-12, SF-12), functional outcomes and mobility (Western Ontario McMaster Osteoarthritis Index, WOMAC, and Timed Up and Go Test, TUG), and health outcome measures (EuroQol-5 Dimensions, EQ-5D).
2. To evaluate the effect of total hip arthroplasty versus hemi-arthroplasty on mortality.
3. To evaluate the effect of total hip arthroplasty versus hemi-arthroplasty on hip-related complications including:
  - Peri-prosthetic fracture
  - Hip instability or dislocation
  - Implant failure (loosening/subsidence and breakage)
  - Wound healing problems (including superficial/deep infection, wound necrosis)
  - Soft tissue problems (i.e. pseudotumor)
  - Heterotopic ossification
  - Abductor failure
  - Implant wear and corrosion
  - Osteolysis
  - Neurovascular injury
  - Decreased function
  - Pain

### **3. STUDY DESIGN**

#### **3.1 Study Overview**

HEALTH is a multi-centre, concealed ‘expertise-based’ randomized trial of 1,434 patients who have sustained a displaced femoral neck fracture. Minimization will be used to determine patient allocation. Surgeons across North America, Europe, Australia, and Asia will participate. In conventional surgical hip fracture trials, all surgeons involved in the trial have performed both total hip arthroplasties and hemi-arthroplasties based on the randomization process (**Figure 4**). HEALTH will utilize an alternative randomized trial design that allocates patients to surgeons with expertise in total hip arthroplasty or hemi arthroplasty (**Figure 5**). Based upon their expertise, surgeons will use one of two surgical strategies in patients who have sustained a displaced femoral neck fracture. The first strategy involves total hip arthroplasty (i.e., replacement of the femoral head and hip socket). The second treatment strategy involves a hemi-arthroplasty (i.e., replacement of the femoral head only).

Study personnel will monitor critical aspects of peri-operative care and rehabilitation. Patients will be assessed at hospital admission (baseline), 1 week, 10 weeks, 6 months, 9 months, 12 months, 18 months, and 24 months after surgery. Fracture eligibility, technical placement of prostheses, secondary procedures, hip-related complications, and deaths will be independently adjudicated.

##### 3.1.1 Expertise-Based Randomized Controlled Trial

HEALTH will utilize an alternative randomized trial design that allocates patients to surgeons with expertise in total hip arthroplasty who are committed to performing total hip arthroplasty, or to surgeons with expertise in hemi-arthroplasty who are committed to performing hemi-

arthroplasty (**Figure 5**). Those surgeons who feel confident enough in both will perform both total hip arthroplasty and hemi-arthroplasty. Devereaux and colleagues have outlined the advantages of this trial design, which include the following:

1. Elimination of differential expertise bias in which, in conventional designs, a larger proportion of surgeons are expert in one procedure under investigation than the other.
2. Differential performance, co-intervention, data collection, and outcome assessment are less likely than in conventional RCT.
3. Procedural crossovers are less likely because surgeons are committed and experienced in their procedures.
4. Ethical concerns are reduced because all surgeries are conducted by surgeons with expertise and conviction concerning the procedure (Devereaux et al, 2005).

### **3.2 Proposed Primary and Secondary Outcome Measures**

#### 3.2.1 Primary Outcomes

The primary outcome is any unplanned secondary procedure within 2 years of the initial joint replacement surgery. A Central Adjudication Committee will review each reported secondary procedure to determine that they are study events (i.e. unplanned) and they will confirm the type of the procedure and the reason for the procedure (**Table 1**).

Specific unplanned secondary procedures include:

1. Closed reduction of hip dislocation
2. Open reduction of hip dislocation
3. Open reduction of fracture
4. Soft tissue procedure
5. Insertion of antibiotic spacer
6. Full implant exchange
7. Partial implant exchange – stem only
8. Partial implant exchange - head only
9. Partial implant exchange - liner only
10. Partial implant exchange - head and liner
11. Partial implant exchange – acetabular component only
12. Partial implant exchange – acetabular component and head
13. Implant adjustment – re-orientation of the stem
14. Implant adjustment – re-orientation of the acetabulum component
15. Implant removal with no replacement
16. Excision heterotopic ossification
17. Supplementary fixation

Classification of the reason for secondary procedures is as follows:

1. Treat a peri-prosthetic fracture
2. Treat hip instability or dislocation
3. Treat infection – superficial
4. Treat infection – deep
5. Treat wound necrosis
6. Treat another wound healing problem

7. Remove heterotopic ossification
8. Manage abductor failure
9. Manage another soft tissue problem (i.e. pseudotumor)
10. Correct implant failure –loosening or subsidence
11. Correct implant failure - breakage
12. Treat implant wear
13. Treat osteolysis
14. Treat implant corrosion
15. Improve function
16. Relieve pain

### 3.2.2 Secondary Outcomes

Secondary outcomes will include:

Functional outcome and quality of life will be measured using self-administered and interview-administered questionnaires. Functional outcome questionnaires will include a generic health status measurement instrument (SF-12), a hip function and pain questionnaire (WOMAC), a health outcome measure (EQ-5D), and a functional mobility test (TUG). HEALTH will further report the effect of total hip arthroplasty versus hemi-arthroplasty on mortality and hip-related complications including:

- Peri-prosthetic fracture
- Hip instability or dislocation
- Implant failure (loosening/subsidence and breakage)
- Wound healing problems (including superficial/deep infection, wound necrosis)
- Soft tissue problems (i.e. pseudotumor)
- Heterotopic ossification
- Abductor failure
- Implant wear and corrosion
- Osteolysis
- Neurovascular injury
- Decreased function
- Pain

At 1 week, 10 weeks, 6 months, 12 months, and 24 months after surgery the research coordinator or nurse will ascertain patient status via clinic visits and completion of self-administered quality of life forms (SF-12, WOMAC, and EQ-5D) and the functional mobility test (TUG) (**Figure 7**). During all visits the research coordinator or nurse should be prepared to conduct interview-administered data collection if patients are unable to complete the self-administered forms. Hip-related complications will also be documented at each follow-up. Other serious adverse events and non-hip related complications will also be recorded (refer to section 9.0). At 9 months and 18 months after surgery the research coordinator or nurse will ascertain patient status (i.e., secondary procedures, hip-related complications, deaths), as well as administer quality of life questionnaires (SF-12, WOMAC, and EQ-5D) via telephone calls and verifying information in medical records.

The **SF-12** questionnaire was developed from the Medical Outcomes Study (McHorney et al, 1992). It is a self-administered, 12-item questionnaire that measures health-related quality of life in 8 domains. Both physical and mental summary scores can be obtained. Each domain is scored separately from 0 (lowest level) to 100 (highest level) (Ware et al, 1996).

The **WOMAC** index is self-administered and assesses the three dimensions of pain, disability and joint stiffness in knee and hip osteoarthritis using a battery of 24 questions (Bellamy et al, 1988).

The **EQ-5D** is a comprehensive, compact health status classification and health state preference system (Brooks et al, 2003). Patients who are completing the self-administered version of the EQ-5D will also be asked to complete a test version of the EQ-5D questions that uses 5-level response options. This data will be used in a sub-study comparing the test version to the validated version, which uses 3-level response options.

The **TUG** is a simple test that involves documenting the time, in seconds, taken for subjects to “rise from a standard arm chair, walk to a line on the floor 3 meters away, turn, return, and sit down again” (Podsiadlo and Richardson, 1991).

## **4. SUBJECT SELECTION AND RISK**

### **4.1 Inclusion and Exclusion Criteria**

#### 4.1.1 Inclusion Criteria

1. Adult men or women aged 50 years and older (with no upper age limit).
  2. Fracture of the femoral neck confirmed with either anteroposterior or lateral hip radiographs, computed tomography, or magnetic resonance imaging (MRI).
  3. Displaced fracture that is not, in the judgment of the attending surgeon, optimally managed by reduction and internal fixation.
  4. Operative treatment within 3 days (i.e. 72 hours) of the patient being medically cleared for surgery.
  5. Patient was ambulatory prior to fracture, though they may have used an aid such as a cane or a walker.
  6. Anticipated medical optimization for arthroplasty of the hip.
  7. Provision of informed consent by patient or proxy.
  8. Low energy fracture (defined as a fall from standing height).
  9. No other major trauma (defined as an Injury Severity Score <17\*).
  10. Assurance that surgeons with expertise in both total hip arthroplasty and hemi-arthroplasty are available to perform surgery. Note: Surgeons do not need to be experts in both techniques.
- \*The Injury Severity Score (ISS) is an anatomical scoring system that provides an overall score for patients with multiple injuries. Each injury is assigned an Abbreviated Injury Scale (AIS) score and is allocated to one of six body regions (Head, Face, Chest, Abdomen, Extremities (including Pelvis), and External). Only the highest AIS score in each body region is used. The 3 most severely injured body regions have their score squared and added together to produce the ISS score. More information can be found at: <http://www.trauma.org/archive/scores/iss.html>.

#### 4.1.2 Exclusion Criteria

1. Patient not suitable for hemi-arthroplasty (e.g. inflammatory arthritis, rheumatoid arthritis, pathologic fracture (secondary to cancer), or severe osteoarthritis of the hip).
2. Associated major injuries of the lower extremity (i.e., ipsilateral or contralateral fractures of the foot, ankle, tibia, fibula, knee, or femur; dislocations of the ankle, knee, or hip; or femoral head defects or fracture).
3. Retained hardware around the affected hip that will interfere with arthroplasty.
4. Infection around the hip (soft tissue or bone).
5. Patients with a disorder of bone metabolism other than osteoporosis (i.e., Paget's disease, renal osteodystrophy, osteomalacia).
6. Patients with a previous history of frank dementia that would interfere with assessment of the primary outcome (i.e., secondary procedures at 2 years).
7. Likely problems, in the judgment of the investigators, with maintaining follow-up (i.e., patients with no fixed address, report a plan to move out of town, or intellectually challenged patients without adequate family support).
8. Patients whose fracture occurred as a result of an act of violence.

For Item 6 above, patients with a history of frank dementia are unlikely to survive to 2 years, which will cause problems with assessment of the primary outcome.

Exclusion of a patient because of enrolment in another ongoing drug or surgical intervention trial will be left to the discretion of the attending surgeon, on a case-by-case basis.

## **5. STUDY INTERVENTIONS**

### **5.1 Arthroplasty Procedures**

#### 5.1.1 Total Hip Arthroplasty

To optimize feasibility and applicability of results, this study will not standardize the surgical approach, the use of cemented components, the implant manufacturer, or femoral head size. Surgeons will use the manufacturer specific implant guides and jigs for insertion of the total joint arthroplasty. Proscribed approaches will include minimally invasive total hip arthroplasty (i.e., 2 incision approaches) and hinged prostheses or capture cups.

#### 5.1.2 Hemi-Arthroplasty

Surgeons will use modern implants for hemi-arthroplasty excluding non-modular, non-canal filling unipolar implants such as Moore's and Thompson's prostheses. The choice of modular unipolar versus bipolar hemi-arthroplasty will not be standardized. This study will not standardize whether implants are inserted with cement or with a press-fit design. Surgeons will use the manufacturer specific implant guides and jigs for insertion of the total joint arthroplasty. The manufacturer, implant material, and bearing surface of the implant will be documented in all patients.

## **5.2 Standardization of Procedures and Peri-Operative Care**

Given the inherent variability in practice patterns among orthopaedic surgeons, it is important to ensure that surgeons adhere as closely as possible to the surgical management protocol and to current accepted practice.

To ensure that all participating surgeons perform their respective procedures in a similar manner, they will be required to review training materials that highlight critical aspects of the surgical protocols which are posted on the HEALTH trial website ([clarityrand.mcmaster.ca/HEALTH](http://clarityrand.mcmaster.ca/HEALTH)).

Several strategies will be instituted to ensure adherence to the protocol, including the following:

1. Interactive educational sessions or presentations with orthopaedic trainees, nurses, and fellows at the beginning of their rotations.
2. Daily reminders (i.e., email and verbal, as well as posters and pocket cards) for on call surgeons by the site research coordinator.
3. Weekly quality control report forms to flag protocol violations.
4. Monthly newsletters re-emphasizing important aspects of the protocol and highlighting compliance figures across all participating sites.
5. Personal telephone calls from the principal investigator or project coordinator to site investigators when protocol violations occur.
6. 24-hour mobile phone contacts for any queries regarding the study protocol.
7. Frequent investigator's meetings to discuss protocol violations and strategies to improve adherence.
8. An active trial website with information updates.

### 5.2.1 Threshold Performance for Expertise in Total Hip Arthroplasty and Hemi-Arthroplasty

Surgeons participating in the HEALTH trial are required to meet both of the following 2 criteria for expertise for either total hip arthroplasty or hemi-arthroplasty:

1. Surgeons must have performed at least 50 procedures (either THA or HA) in their career (including residency experience in which they assumed responsibility for the procedure).
2. Surgeons must continue to perform at least 5 procedures (either THA or HA) in the year prior to trial start date, as well as each year for the duration of the study.

Surgeons who meet the threshold for both total hip arthroplasty and hemi-arthroplasty will perform both procedures if no overwhelming bias in favour of one procedure is evident. A surgeon will be considered biased for an approach if he/she has performed less than 5 cases of either procedure in his/her last 50 procedures for a displaced femoral neck fracture.

Residents and fellows may perform the procedures under the supervision of a participating attending surgeon. The surgeon most responsible for the case must meet threshold expertise criteria and must be present in the operating room for the critical aspects of the procedure (**Table 2**).

### 5.2.2 Peri-Operative and Post-Operative Treatment Common to Both Groups

To ensure similar peri-operative regimens, it is recommended that participating centres standardize key aspects of pre- and post-operative care.

### 5.2.3 Pre-Operative Care

1. Pre-operative antibiotic prophylaxis (i.e., cephalosporin, Ancef, or equivalent coverage).
2. Thromboprophylaxis (i.e., Thromboembolic Disease Stockings (TEDS), pneumatic compression boots, or medical prophylaxis to be discontinued in sufficient time to allow surgery as guided by International Normalized Ratio (INR) / Partial Thromboplasty Time (PTT)).
3. Medical consultation to optimize condition prior to surgery.

### 5.2.4 Post-Operative Care

1. Antibiotic prophylaxis (i.e., cephalosporin or equivalent) for 24 hours.
2. Thromboprophylaxis with unfractionated heparin, Low Molecular Weight Heparin (LMWH), warfarin, anti-platelet agents, or intermittent pneumatic compression boots.
3. Weightbearing as tolerated will be allowed as patients autoprotect the affected hip during rehabilitation. Post-surgery, patients will be weightbearing as tolerated, and then advanced according to the attending surgeon's best judgment (i.e., touch weightbearing will be permitted, and then advanced according to the surgeon's best judgment).
4. Calcium 600 mg by mouth (PO) daily and vitamin D 1000 International Units (IU) per day (provided there are no contraindications) and further investigation and treatment of osteoporosis as recommended by a local osteoporosis expert/consultant.
5. Appropriate nutritional assessment with administration of oral micronutrient feeds as needed.

### 5.2.5 Other Care

Due to a lack of evidence favouring a particular approach, the following will be recorded but not standardized:

1. Use of pre-operative traction.
2. Surgical delay.
3. Type of anesthetic (i.e., general or regional).
4. Physiotherapy and rehabilitation programs.

## **6. STUDY PROCEDURES**

### **6.1 Patient Screening**

All patients presenting to participating surgeons with a diagnosed displaced femoral neck fracture amenable to arthroplasty will be screened. Such patients will be classified as:

1. Excluded (if they subsequently do not meet the eligibility criteria).
2. Missed (due to error or staff availability).
3. Eligible and randomized (if applicable).

If the participating surgeon identifies the eligible patient who consents to randomization, the surgeon or delegate will contact the automated computer randomization system by Internet (see Section 6.2) (**Figure 6**). The surgeon or delegate will enter in the patient's prognostic factors (Section 6.2). The automated system will then allocate the patient into 1 of 2 groups (total hip arthroplasty or hemi arthroplasty).

## 6.2 Randomization

Allocation will be concealed using a centralized 24-hour computerized randomization system that will allow Internet-based randomization. Patients will be the unit of randomization. To protect against prognostic imbalance between groups, minimization will be used to ensure balance between intervention groups for several patient factors. The minimization approach measures marginally each prognostic variable and sums over the variables.

Unlike random permuted block within strata, minimization works toward minimizing the total imbalance for all factors together instead of considering mutually exclusive subgroups (Pocock, 2005). Based upon our international survey of surgeons (Bhandari et al, 2005), and current evidence (Gillespie, 2001), we will minimize for the following prognostic factors:

1. Age (i.e., 50-80 years or >80 years).
2. Pre-fracture living setting (i.e., institutionalized or not institutionalized).
3. Pre-fracture functional status (i.e., using aid or independent ambulator).
4. American Society for Anesthesiologists (ASA) Class (i.e., Class I/II or III/IV/V).
5. Centre number.

## 6.3 Frequency and Duration of Follow-up

All patients will be followed for a period of 2 years (**Figures 6 and 7**). In addition, at the 2-year follow-up visit, the surgeon will document any secondary procedures that may be planned for the patient. Clinical assessments will occur at the time of admission to hospital (baseline), 1 week (24 hours – 10 days window), 10 weeks (8-12 weeks window), 6 months (5-7 months window), 12 months (11-13 months window), and 24 months ( $\geq 24$  months window) after surgery. X-rays will be taken at the time of admission to hospital (baseline), within 48 hours post surgery, and at 10 weeks (8-12 weeks window), 12 months (11-13 months window), and 24 months ( $\geq 24$  months window) post surgery. At 9 months (8-10 months window) and 18 months (17-19 months window) after surgery the research coordinator or nurse will ascertain patient status (i.e., secondary procedures, hip-related complications, deaths, as well as interview-administered quality of life questionnaires (SF-12, WOMAC, and EQ-5D)) via telephone calls and verifying information within medical records. At 1 week (24 hours – 10 days window), 10 weeks (8-12 weeks window), 6 months (5-7 months window), 12 months (11-13 months window), and 24 months ( $\geq 24$  months window) post surgery the research coordinator or nurse will ascertain patient status via clinical visits and completion of self-administered quality of life questionnaires (SF-12, WOMAC, and EQ-5D), and the functional mobility test (TUG).

## 6.4 Maximizing Patient Follow-up

Previous trials in hip fracture surgery have lost up to 50% of patients to follow-up (Bhandari et al, 2003). To avoid this problem, the strategies outlined in **Figure 8** will be used to minimize loss to follow-up.

## 6.5 Crossovers and Co-interventions

Crossovers are extremely unlikely between total hip arthroplasty and hemi-arthroplasty as patients will be treated by surgeons with expertise to the allocated procedure. Any patients who do cross over will be analyzed in the group to which they were allocated, maintaining the intention to treat approach of the analysis. Surgical co-intervention such as a general, neurosurgical, or orthopaedic procedure may confound outcomes. The standardization of management protocols and the expertise-based trial design will limit co-intervention, and the use of drugs that affect the bone, and major additional procedures that patients undergo will both be recorded. Research coordinators will record all medications such as bisphosphonates, vitamin D, calcium, hormone replacement therapy, selective estrogen receptor modulators, calcitonin, and anabolic steroid therapy used concurrently in included patients.

### **6.6 Differential Expertise Bias**

The HEALTH trial design will eliminate differential expertise bias by establishing a minimal threshold for expertise, as well as ensuring that all surgeons performing either hemi-arthroplasty or total hip arthroplasty are dedicated to and expert in the procedure.

### **6.7 Adjudication of Events**

An independent Central Adjudication Committee (CAC) will review cases where fracture eligibility is in doubt and the technical placement of prostheses. They will also review secondary procedures and hip-related complications, and will decide if a secondary procedure and/or hip-related complication meeting study criteria has occurred. Planned secondary procedures will not be considered study events. The CAC will also review cases of mortality. Adjudication will occur after patients have completed their 2 year follow-up. Any disagreements among the CAC members will be resolved during monthly conference calls. The CAC will include 3 orthopaedic surgeons who specialize in orthopaedic trauma and have expertise in research methodology and experience with clinical trials.

All centres will submit digital x-rays to the Methods Centre, and fax all relevant hospital records. All relevant patient records devoid of personal identifiers (i.e., DataFax forms, chart notes, and x-rays) will be posted on a specially designed, and password protected, Internet website for study adjudication. Additional information will be requested from the participating site to clarify areas of uncertainty. All decisions made by the committee will be final.

### **6.8 Blinding**

While surgeons, patients, and outcome assessors cannot be blinded to the surgical arms (i.e., total hip arthroplasty or hemi-arthroplasty), data analysts will remain blinded throughout the trial. The primary outcome (secondary procedures) is objective and lack of blinding introduces minimal threats to validity.

## **7. STATISTICAL PLAN**

## 7.1 Sample Size Determination

The choice of sample size is based upon a comparison for the primary outcome (secondary procedures) of THA versus HA. All statistical hypotheses will be two-sided. Alpha levels of 0.05 for the primary and 0.01 for the secondary outcomes were chosen. Previous studies have reported secondary procedure rates in hip fracture patients treated with HA that have ranged from 4 to 10% at one year, with a weighted pooled risk of 5.3% (95% CI 3.2 to 8.9%) in a fixed effect meta-analysis, or 4.9% (95% CI 2.6 to 9.2%) using random effects. A pooled estimate from 5 randomized trials comparing THA with HA gave a relative risk of 1.67 (95% CI 0.86 to 3.24,  $p=0.13$ ) (**Table 3a**).

The sample size calculation reflects the proposed approach to the primary analysis, which will use the Cox proportional hazards model. The calculation is based on methods described by Collett (Collett, 1994). The goal is to calculate the required number of patients that will yield a sufficient number of outcome events (secondary procedures) in order to have adequate statistical power for a given size of treatment effect. This was done taking into account the anticipated secondary procedure rates in the HA group, postulated values of the relative risk increase associated with THA vs. HA, and the rates of mortality and loss to follow-up. Because some of these inputs are expected to change over the two year period of follow-up, the expected number of person-years of follow-up and the expected numbers of study events in each group were calculated, initially for the first year of follow-up; the calculation was then repeated for the second year of follow-up, after having estimated the number of patients in each group who would survive, be event-free, and available for continued follow-up between 12 and 24 months post-randomization.

Based upon aggregate data from the pilot study, annual mortality rates of 15% and a loss to follow-up of 5% in each group were assumed, these rates applying to each of the two years of follow-up. Informed by the meta-analysis, the following assumptions were made: a one year risk of having a secondary procedure of 5% in the HA group and a risk of 1% in the second year. Various values of the relative risk reduction (HA vs. THA) were then used to identify the specific value that would correspond to a cumulative risk difference between THA and HA of 5% after 2 years. This figure was identified in a survey of participating surgeons as the minimally important difference to clinicians. Annual event risks by group were converted into equivalent hazard rates, assuming for simplicity that the hazard rate would be approximately constant within each of the two years. It is estimated that approximately 72% of the group receiving THA and 76% of the group receiving HA will be event-free and available for further follow-up at the start of the second year. The sample size was increased to allow for a combined 7.6% crossover rate from the assigned to the alternate treatment, based on pilot data. These assumptions lead to a required total sample size of 1,316 patients, which will yield an expected number of 96 secondary procedures. The associated relative risk reduction (RRR) is 0.45.

These calculations were repeated after replacing the 5% event risk at one year for HA by 4% and 6% and leaving the other factors unchanged (**Table 3b**). To account for potential surgeon level effects, the sample size has been further increased by 9% to 1,434.

For the secondary outcomes, an important difference in SF-12 is considered to correspond to a moderate effect as reported by Cohen (Cohen, 1988) as well as a minimally important difference in the SF-12 as reported by Ware (Ware & Sherbourne, 1992). In both cases, the value is at least half the standard deviation, equivalent to 4-point difference in score. Specifying an alpha level=0.05, a beta=0.20 (study power=80) and a standard deviation of 8 (Jaglal et al, 2000), a sample of at least 128 patients (64 per group) is required to ensure detection of a half standard deviation improvement. In clinical drug trials, a 9-point change in WOMAC functional score was accepted as a minimally significant improvement in symptoms (Turbach et al, 2005). In this study, at least 90 patients (45 per group) would be required to detect this difference (alpha level=0.05, beta=0.20,  $\sigma = 15$ ). Previous studies have found a standard deviation of 0.20 for the EQ-5D (Tidermark et al, 2003). To detect a difference of 0.10 (half the standard deviation) with 80% power at an alpha level of 0.05, this study requires a total of 128 patients (64 per group). Thus, in all circumstances, the desired sample size of **1,434 patients** will be sufficient to detect clinically meaningful differences in the secondary measures of outcome.

## 7.2 Statistical Methods

### 7.2.1 Primary Analyses

All outcome analyses will be performed by an intention to treat approach. To evaluate the effect of total hip arthroplasty versus hemi-arthroplasty on time to secondary procedures (the primary outcome), a Cox proportional hazards model will be used with the following covariates:

1. Age (i.e., 50-80 years or >80 years).
2. Pre-fracture living setting (i.e., institutionalized or not institutionalized).
3. Pre-fracture functional status (i.e., using aid or independent ambulator).
4. American Society for Anesthesiologists (ASA) Class (i.e., Class I/II or III/IV/V).
5. Centre number.

Results will be reported as hazard ratios with 95% confidence intervals. Kaplan-Meier curves will be constructed.

### 7.2.2 Secondary Analyses

A generalized linear model will estimate the effect of total hip arthroplasty versus hemi-arthroplasty on quality of life (SF-12), function (WOMAC), health outcome (EQ-5D), and mobility (TUG) at follow-up using the following covariates that are included in our minimization procedure:

1. Age (i.e., 50-80 years or >80 years).
2. Pre-fracture living setting (i.e., institutionalized or not institutionalized).
3. Pre-fracture functional status (i.e., using aid or independent ambulator).
4. American Society of Anesthesiologists (ASA) Class (i.e., Class I/II or III/IV/V).
5. Centre number.

Cox proportional hazards modeling will estimate the relative effect of total hip arthroplasty versus hemi-arthroplasty on time to mortality and hip-related complications. Results will be reported as hazard ratios with 95% confidence intervals. Kaplan-Meier curves will be constructed.

### 7.2.3 Planned Subgroup Analyses

There are no planned subgroup analyses.

### 7.2.4 Frequency of Analysis

The approach to interim analyses is guided by a desire to avoid spuriously inflated estimates of treatment effect (Montori et al, 2005; Briel et al, 2009). A single interim analysis will be performed when 60% of the planned patient-years of follow-up have been accrued. The data analyst will present the results of these analyses to our independent Data Monitoring Committee (see Section 8.4). The committee will be guided by the O'Brien-Fleming stopping rule based on the primary outcome, which will maintain the overall specified type I error rate at 5% for the combined interim and final analyses. According to this rule, the required p-value to declare a significant result at the interim analysis is 0.00762, and at the final analysis, the required p-value is 0.0476. The rule is conservative, making it difficult to stop the trial early unless a large treatment effect is observed. We will only apply our stopping rule to the primary outcome. The secondary functional outcomes may demonstrate significance quickly due to the nature of the instruments, but we will not stop the study for that reason. No one other than committee members will be aware of the data on which the committee makes its decision, and no one involved in the study will be aware of the content of their deliberations.

### 7.2.5 Economic Analysis

Including an economic analysis in the current proposal will substantially increase the resource requirements. To ensure the future feasibility of an economic analysis, patient utilities will be collected utilizing the EQ-5D and a separate proposal for additional funds will be developed to conduct a full economic analysis.

## **8. DATA HANDLING AND RECORD KEEPING**

### **8.1 Confidentiality**

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

1. what protected health information (PHI) will be collected from subjects in this study,
2. who will have access to that information and why,
3. who will use or disclose that information, and
4. the rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

### **8.2 Case Report Forms**

The CRFs are the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write “N/D”. If the item is not applicable to the individual case, write “N/A”. All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated.

### **8.3 Data Management**

Data from the case report forms will be entered into the study’s electronic data capture system (iDataFax). Upon receipt of the data, the staff at the Methods Centre will make a visual check of each form. Methods Centre personnel will query all missing data, implausible data, and inconsistencies. Frequent reports summarizing all queries will be sent to the research coordinators from each clinical centre by email. The quality control report will include the following:

1. Patients entered into the trial.
2. Completed follow-up visits.
3. Outstanding data clarification requests.
4. Date when patient’s next follow-up visit is due.
5. Overdue assessments.

Follow-up telephone calls will be made frequently to ensure problems are corrected. Once problems have been resolved and the case report forms are deemed complete and accurate, the data are marked clean in the iDataFax system. The system has built-in range and logic checks. When logic errors have been corrected, the information is entered into the master file containing data suitable for analysis.

### **8.4 Data Monitoring Committee**

The Data Monitoring Committee (DMC) will be comprised of at least 4 members who remain completely independent of the study investigators and have never received any honoraria from, or held stock in any of the manufacturers whose products are used in this trial. The DMC members will span the spectrum from clinical experts with prior trial experience, a clinical trial methodologist, and a biostatistician. The DMC function in an advisory rather than executive capacity and its duties are detailed in **Table 4**.

When the DMC decide that a definitive answer to the trial question has been achieved (in terms of efficacy, safety, or futility) they will unblind the Principal Investigator. These terms of reference and functions are derived from the principles established by the Data Monitoring Committees: Lessons, Ethics, Statistics (DAMOCLES) Study Group charter. They have been approved by the ethics committees and implemented successfully in several international multi-centre trials.

## **9. SAFETY AND ADVERSE EVENTS**

### **9.1 Definitions**

#### **Adverse Event (AE)**

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 (SAE)**

Adverse events are classified as serious or non-serious. A **serious adverse event** is any AE that is:

1. fatal,
2. life-threatening,
3. requires or prolongs hospital stay,
4. results in persistent or significant disability or incapacity,
5. a congenital anomaly or birth defect, or
6. an important medical event.

#### **Unanticipated Problems Resulting in Risk to Subjects or Others**

Any incident, experience, or outcome that meets all of the following criteria:

1. unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc.),
2. related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research),
3. suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

Unanticipated problems resulting in risk to volunteers or others encompass more than what one usually thinks of as adverse events. “Problems involving risk” may not necessarily result in harm. For example, misplacing a volunteer’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 volunteer that puts study staff at risk would be a reportable event.

### **9.2 Reporting of Serious Adverse Events and Unanticipated Problems Resulting in Risk to Subjects or Others**

All serious adverse events and unanticipated problems resulting in risk to subjects or others are to be reported to the Methods Center immediately.

#### **9.2.1 Investigator Reporting: Notifying the Methods Center**

Any AEs and SAEs must be reported promptly to the Methods Center by completing the AE Form or SAE Form (as applicable) and submitting it via iDataFax or email. The investigator will

keep a copy of this AE/SAE Form on file at the study site. The AE/SAE form should include a written narrative and any other information that will assist the understanding of the event. Significant new information on ongoing Serious Adverse Events should be provided promptly to the Methods Center by updating the AE/SAE form. Unanticipated problems resulting in risk to subjects or others are to be reported to the Methods Center by either fax or email.

#### 9.2.2 Site Investigator – IRB/REB Reporting

Investigators are responsible for reporting AEs, SAEs, and unanticipated problems resulting in risk to subjects or others to their local IRB/REB. Investigators are responsible for complying with their local IRB's/REB's reporting requirements. Copies of each report and documentation of IRB/REB notification and receipt will be kept in the investigator's study file.

### **10. ETHICAL CONSIDERATIONS**

This protocol and any amendments will be submitted to a properly constituted independent REB or IRB, in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the REB/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the Methods Center before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. The consent form will be submitted with the protocol for review and approval by the REB/IRB for the study. The formal consent of a subject, using the REB/IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or legally authorized representative, and the investigator-designated research professional obtaining the consent.

**Table 1: Classification of Types and Reasons for Unplanned Secondary Procedures**

<b>Specific unplanned secondary procedures include:</b>	<b>Classification of the reason for secondary procedures is as follows:</b>
<ol style="list-style-type: none"> <li>1. Closed reduction of hip dislocation</li> <li>2. Open reduction of hip dislocation</li> <li>3. Open reduction of fracture</li> <li>4. Soft tissue procedure</li> <li>5. Insertion of antibiotic spacer</li> <li>6. Full implant exchange</li> <li>7. Partial implant exchange – stem only</li> <li>8. Partial implant exchange - head only</li> <li>9. Partial implant exchange - liner only</li> <li>10. Partial implant exchange - head and liner</li> <li>11. Partial implant exchange – acetabular component only</li> <li>12. Partial implant exchange – acetabular component and head</li> <li>13. Implant adjustment – re-orientation of the stem</li> <li>14. Implant adjustment – re-orientation of the acetabulum component</li> <li>15. Implant removal with no replacement</li> <li>16. Excision heterotopic ossification</li> <li>17. Supplementary fixation</li> </ol>	<ol style="list-style-type: none"> <li>1. Treat a peri-prosthetic fracture</li> <li>2. Treat hip instability or dislocation</li> <li>3. Treat infection – superficial</li> <li>4. Treat infection – deep</li> <li>5. Treat wound necrosis</li> <li>6. Treat another wound healing problem</li> <li>7. Remove heterotopic ossification</li> <li>8. Manage abductor failure</li> <li>9. Manage another soft tissue problem (i.e. pseudotumor)</li> <li>10. Correct implant failure –loosening or subsidence</li> <li>11. Correct implant failure - breakage</li> <li>12. Treat implant wear</li> <li>13. Treat osteolysis</li> <li>14. Treat implant corrosion</li> <li>15. Improve function</li> <li>16. Relieve pain</li> </ol>

**Table 2: Critical Aspects of Operative Procedure Requiring Presence of Experienced Surgeon**

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Hemi-Arthroplasty

- Trial component insertion and verification of hip stability
- Implant insertion to ensure correct version
- Cement procedure, if used
- Final assessment of hip stability after implant insertion

Total Hip Arthroplasty

- Trial component insertion and verification of hip stability
  - Implant insertion to ensure correct alignment of femoral and acetabular components
  - Cement procedure, if used
  - Final assessment of hip stability after implant insertion
-

**TABLE 3: Sample Size Calculations Comparing Total Hip Arthroplasty (THA) and Hemi-Arthroplasty (HA)****A. Studies included in a meta-analysis comparing THA with HA for the outcome of re-operation at one year**

Study	Reoperation Rate	
	THA	HA
van den Bekerom 2010	5/110	1/136
Baker 2006	4/36	2/39
Blomfeldt 2007	4/56	3/57
Keating 2006	6/63	5/64
Macaulay 2008	1/16	0/23

THA vs. HA Combined Effect: fixed and random, relative risk = 1.67 (95% CI 0.86 to 3.24), p=0.13

Pooled Event Rates: THA fixed and random, incidence rate = 7.8% (95% CI 5.2 to 11.6)

HA fixed, incidence rate = 5.3% (95% CI 3.2 to 8.9)

HA random, incidence rate = 4.9% (95% CI 2.6 to 9.2)

**B. Sample size requirement for HEALTH Pivotal Trial [Non-Inferiority Design]**

HA 1 yr event risk	Total patients required	Expected events	RRR
4%	1123	72	0.50
5%	1316	96	0.45
6%	1435	108	0.42

RRR = Relative Risk Reduction

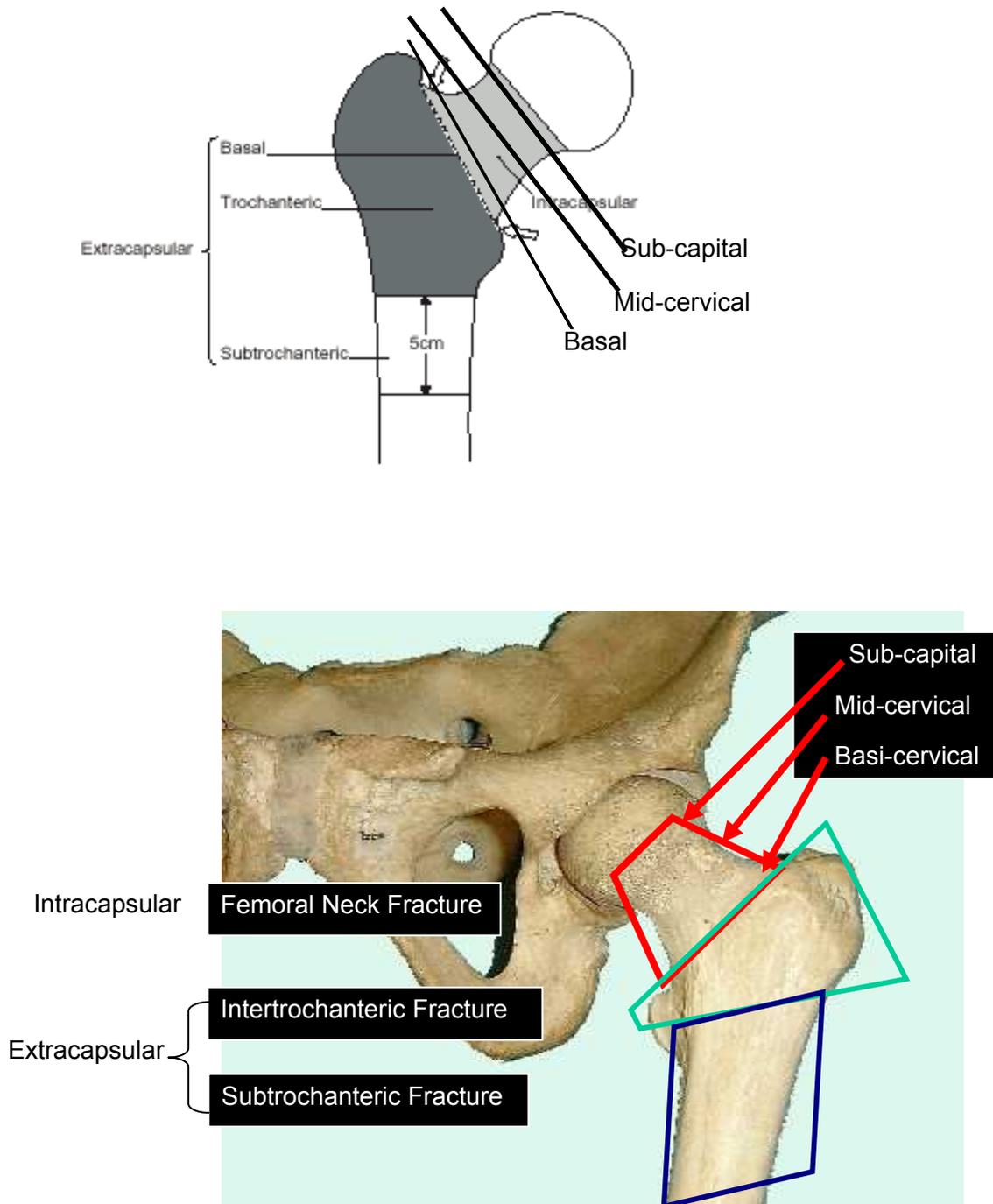
**Table 4: Functions of the Data Monitoring Committee (DMC)**

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The DMC will function in an advisory rather than executive capacity and its duties will include the following:

- Offering advice about the research protocol and proposals for data safety and monitoring, including statistical ‘warning rules’ for efficacy, safety and futility.
  - Evaluating the progress of the trial, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, clinician adherence to the trial protocol and progress toward an orderly completion of the study.
  - Carrying out the rapid evaluation of serious unanticipated adverse events.
  - Evaluating pre-planned interim analyses for efficacy, safety, and the triggering of statistical warning rules. When the DMC decides that a definitive answer to the trial question has been achieved (in terms of efficacy, safety, or futility) they will unblind the Principal Investigator.
-

Figure 1: Anatomy of the Proximal Femur and Fracture Line Level



**Figure 2: Undisplaced and Displaced Femoral Neck Fractures**



I

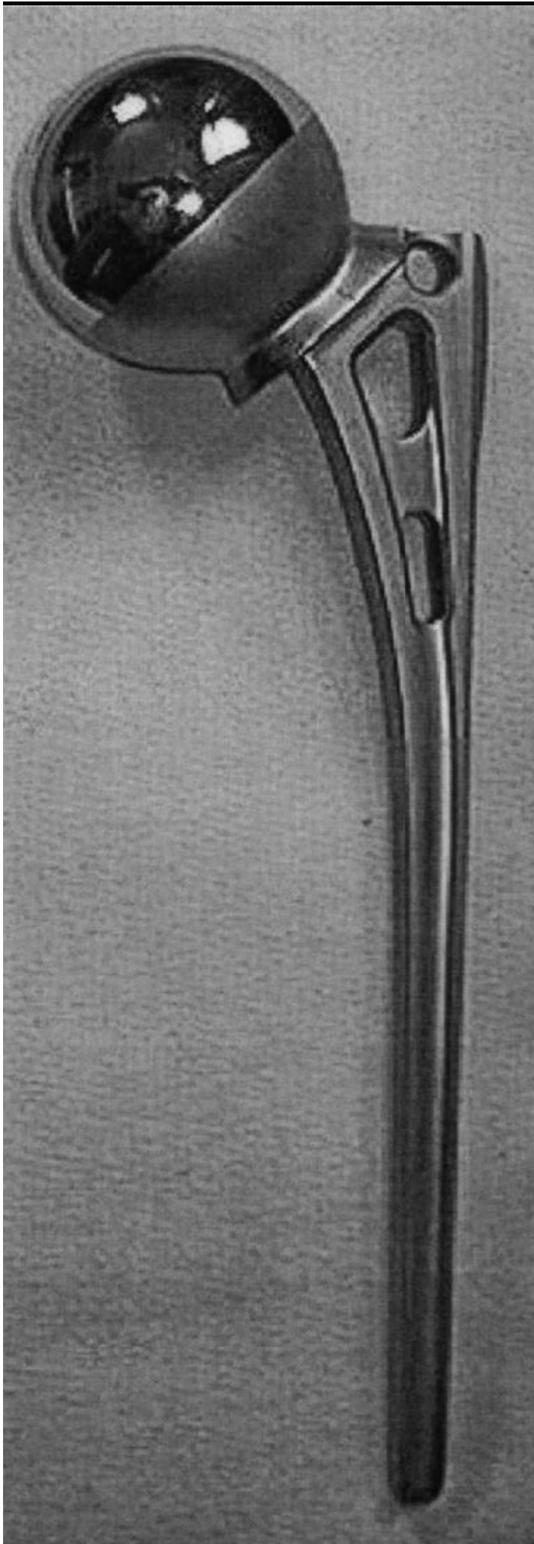
II

III

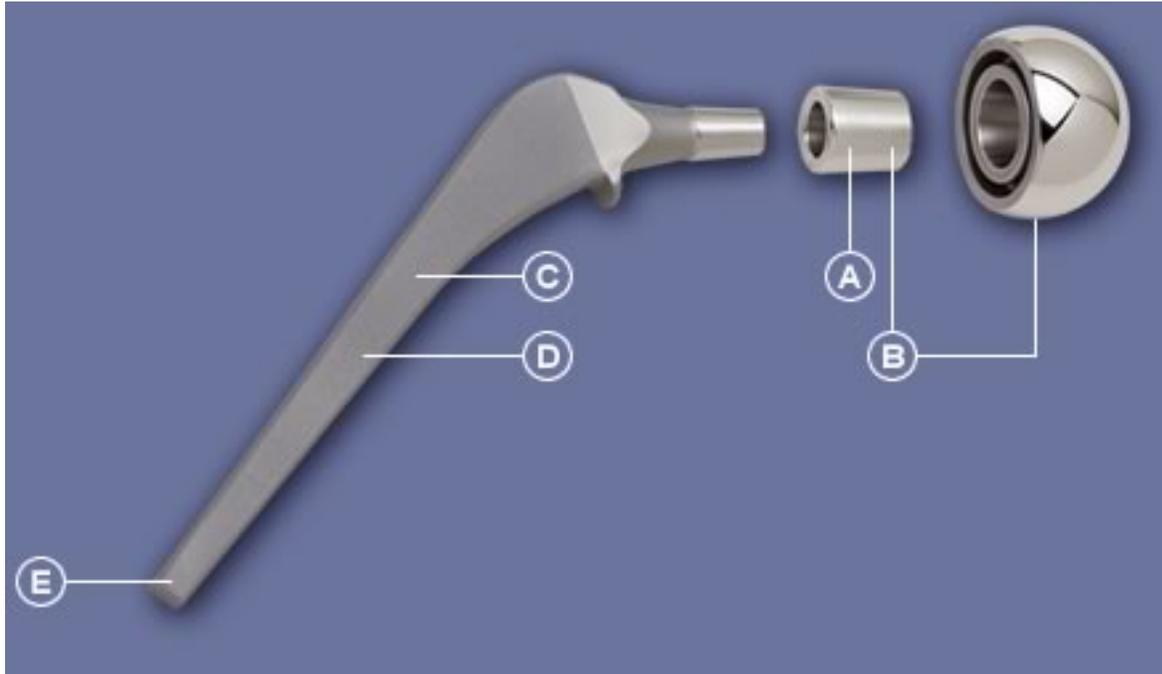
IV

Undisplaced (I, II) and Displaced (III, IV) Femoral Neck Fractures

**Figure 3a. Unipolar Hemi-Arthroplasty Prosthesis**



**Figure 3b. Modular Unipolar Hemi-Arthroplasty Prosthesis**



Legend:

- A = Collar for neck to allow for the metal femoral head component
- B = Tapered neck to allow tight fit to metal femoral head component
- C-E = Metal stem of the femoral component

**Figure 3c. Bipolar Hemi-Arthroplasty Prosthesis**

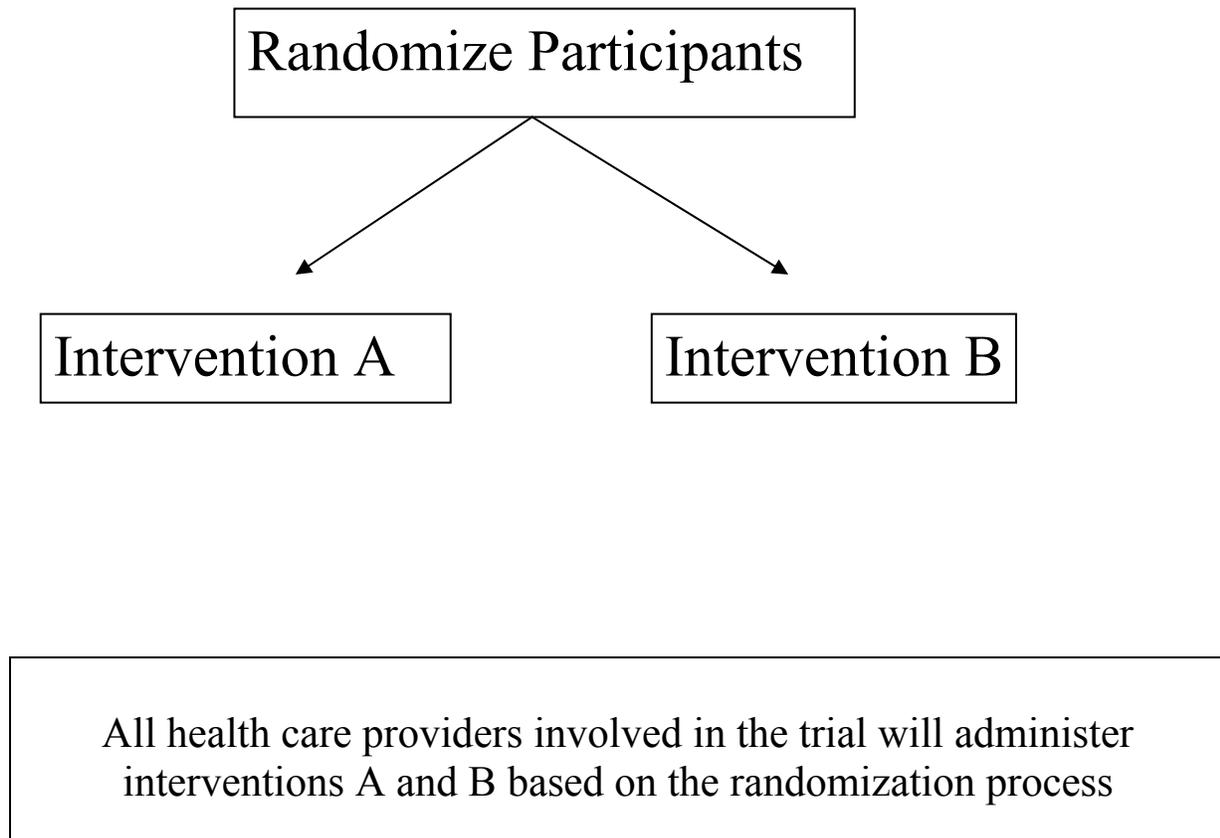


**Figure 3d. Total Hip Arthroplasty Prosthesis**



**Figure 4: Conventional Randomized Controlled Trial**

Conventional randomized controlled trials typically randomize patients to one of two surgeries (A or B), and individual surgeons administer surgery A to some participants and surgery B to others.



**Figure 5: Expertise-Based Randomized Controlled Trial**

An alternative randomized controlled trial design randomizes participants to surgeons with expertise in surgery A who are committed to performing only surgery A or to surgeons with expertise in surgery B who are committed to performing only surgery B.

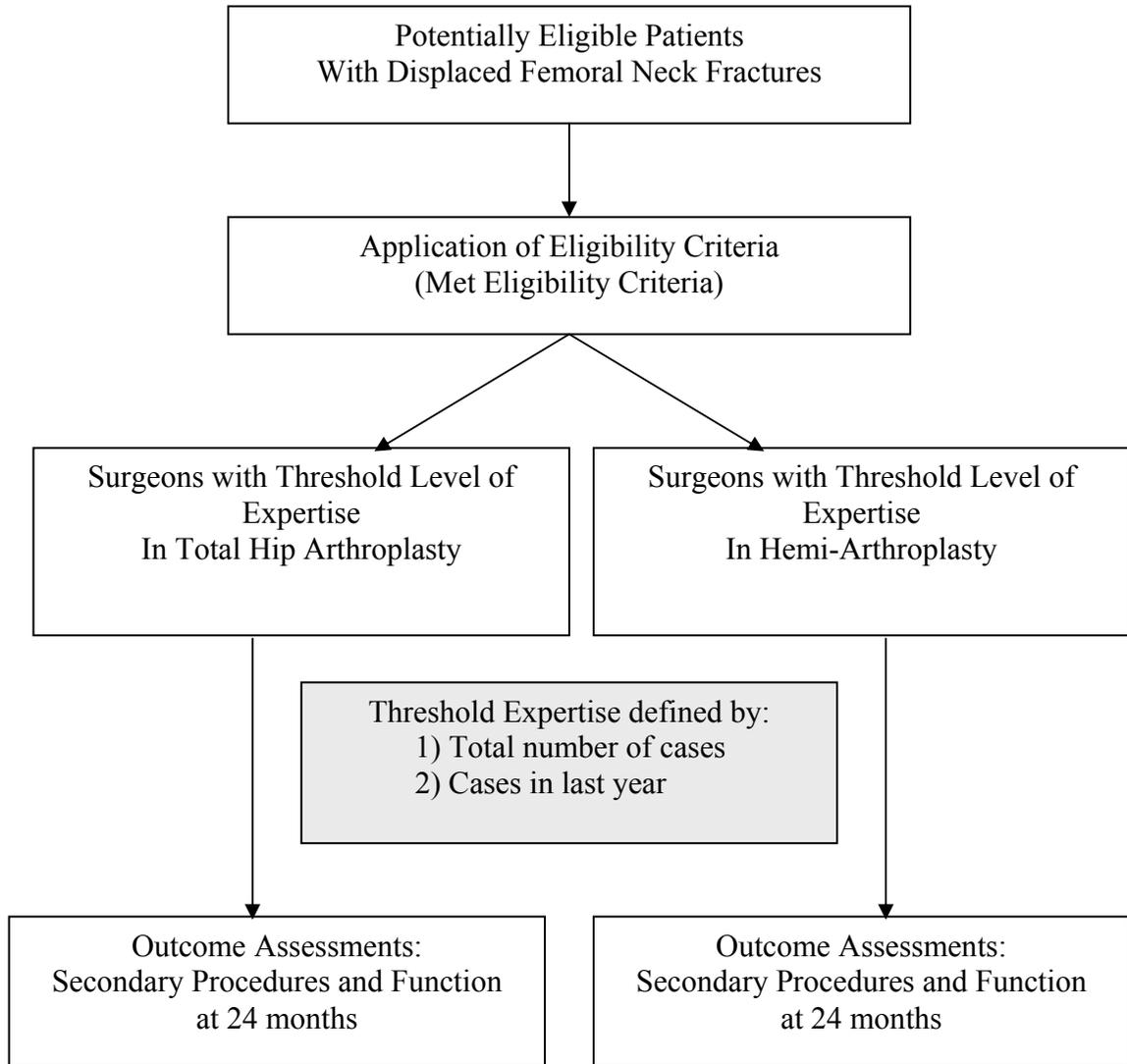


Figure 6: Recruitment Procedures (Baseline Radiographs &amp; Data Collection)

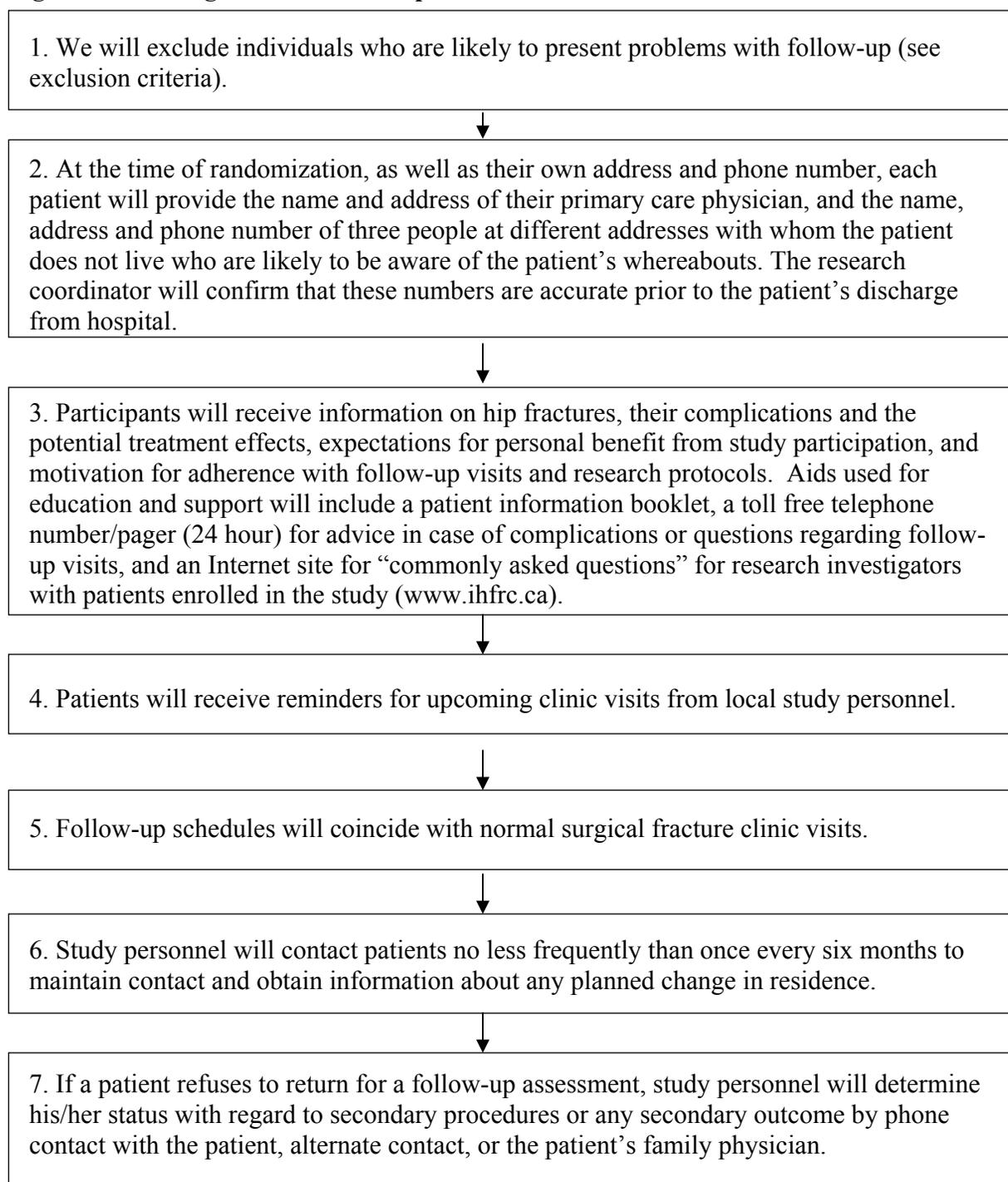
Time Line	Recruitment Procedures	Data Collection
Patient Identification	<ul style="list-style-type: none"> <li>•Direct referral within centre or between centres</li> </ul>	<ul style="list-style-type: none"> <li>•None</li> </ul>
Eligibility Assessment	<ul style="list-style-type: none"> <li>•Study explanation</li> <li>•History-review, eligibility criteria, and other relevant medical conditions documented</li> <li>•Physical Examination</li> <li>•Radiographs</li> <li>•Informed Consent (if eligible)</li> </ul>	<ul style="list-style-type: none"> <li>•Screening Form</li> <li>•Informed Consent</li> <li>•Patient Contact Form</li> <li>•Baseline Form</li> <li>•Fracture Characteristics Form</li> <li>•Pre-op Care Form</li> </ul>
Randomization	<ul style="list-style-type: none"> <li>•24-hour Internet randomization procedure</li> <li>•Eligibility criteria reviewed again</li> <li>•Key patient information recorded at Methods Centre</li> <li>•Allocation issued to patient</li> </ul>	<ul style="list-style-type: none"> <li>•Entry Form at the Methods Centre</li> </ul>
Surgery	<ul style="list-style-type: none"> <li>•Either the total hip arthroplasty or hemi-arthroplasty surgical protocols followed by a surgeon with expertise in the procedure</li> </ul>	<ul style="list-style-type: none"> <li>•Surgical Report Form</li> <li>•Surgical PD Form</li> <li>•AE Form</li> </ul>
Peri-operative Care within 48 hours post surgery	<ul style="list-style-type: none"> <li>•Standardization of key aspect of peri-operative care</li> <li>•Radiographs</li> </ul>	<ul style="list-style-type: none"> <li>•Peri-operative Form</li> <li>•Post-op Care Form</li> <li>•RS, AE Forms</li> </ul>

Figure 7: Post-Surgery Follow-Up Procedures

<b>Time Line</b>	<b>Outcome Events Assessment Procedures</b>	<b>Data Collection</b>
1 week (24 hrs – 10 days window)	In Person/ Hospital/Clinic (if prior to D/C)	•Follow-up Form •SP, AE Forms •SF-12, WOMAC, EQ-5D (self-administered*) (asking about patient function prior to surgery)
	↓	
10 weeks (8-12 weeks window)	In Person/ Hospital/Clinic (if prior to D/C) or Telephone	•Follow-up Form, and TUG Test •SP, AE Forms •SF-12, WOMAC, EQ-5D (self-administered*) •Radiographs
	↓	
6 months (5-7 months window)	In Person/ Hospital/Clinic or Telephone	•Follow-up Form, and TUG Test •SP, AE Forms •SF-12, WOMAC, EQ-5D (self-administered*)
	↓	
9 months (8-10 months window)	Telephone or In Person/ Hospital/Clinic	•Follow-up Form •SP, AE Forms •SF-12, WOMAC, EQ-5D (interview-administered)
	↓	
12 months (11-13 months window)	In Person/ Hospital/Clinic or Telephone	•Follow-up Form, and TUG Test •SP, AE Forms •SF-12, WOMAC, EQ-5D (self-administered*) •Radiographs
	↓	
18 months (17-19 months window)	Telephone or In Person/ Hospital/Clinic	•Follow-up Form •SP, AE Forms •SF-12, WOMAC, EQ-5D (interview-administered)
	↓	
24 months (>24 months window)	In Person/ Hospital/Clinic or Telephone	•Follow-up Form, and TUG Test •SP, AE Forms •SF-12, WOMAC, EQ-5D (self-administered*) •Radiographs •Planned RS after 24 months

\* Prepare for interview-administered data collection if patient unable to complete self-administered forms.

AE = Adverse Event, D/C = Discharge, EQ-5D = EuroQol-5D, SP = Secondary Procedures, SF-12 = Short Form-12, TUG = Timed Up and Go, WOMAC = Western Ontario McMaster Osteoarthritis Index.

**Figure 8: Limiting Loss to Follow-Up****Reference:**

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## Appendix 1: Schedule of Events Requiring Radiographs and Data Forms

Radiographs & Event Forms	Pre-Surgery			Surgery	≤ 48 hrs Post Surgery	D/C	1 wk (24 hrs -10 ds)	10 wk (8-12 wks)	6 mo (5-7 mos)	9 mo (8-10 mos)	12 mo (11-13 mos)	18 mo (17-19 mos)	24 mo (≥24 mos)
	Screening	Enrollment	Baseline	(Day 0)									
Radiographs			●		●			●			●		●
Screening	●												
Informed Consent		●											
Randomization		●											
Baseline			●										
Patient Contact		●			●	●	●	●	●	●	●	●	●
Surgical Report				●									
Post-Op Care					●								
Clinic or Telephone Follow-Up							●	●	●	●	●	●	●
Secondary Procedure					*		*	*	*	*	*	*	*
AE				*	*		*	*	*	*	*	*	*
TUG							●	●	●		●		●
SF-12							●	●	●	●	●	●	●
WOMAC							●	●	●	●	●	●	●
EQ-5D							●	●	●	●	●	●	●
Missed Follow-Up							*	*	*	*	*	*	
Early W/D							*	*	*	*	*	*	*

\* Complete forms when and/or if applicable.