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Hip Fracture Evaluation with ALternatives of Total Hip Arthroplasty versus Hemi-Arthroplasty (HEALTH): Design and Rationale for a Multi-Centre Randomized Trial Comparing Total Hip Arthroplasty and Hemi-Arthroplasty in Patients with Displaced Femoral Neck Fractures

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ABSTRACT

Introduction

Hip fractures are a leading cause of mortality and disability worldwide and the number of hip fractures is expected to rise to over 6 million per year by 2050. The optimal approach for the surgical management of femoral neck fractures remains unknown. Current evidence suggests the use of arthroplasty; however, there is lack of evidence regarding whether patients with displaced femoral neck fractures experience better outcomes with total hip arthroplasty (THA) or hemi-arthroplasty (HA). The HEALTH trial compares outcomes following THA versus HA in patients 50 years of age or older with displaced femoral neck fractures.

Methods and Analysis

HEALTH is a multi-centre, randomized controlled trial where 1,434 patients 50 years of age or older with displaced femoral neck fractures from international sites, are randomized to receive either THA or HA. Exclusion criteria include associated major injuries of the lower extremity, hip infection(s) and a history of frank dementia. The primary outcome is unplanned secondary procedures and the secondary outcomes include functional outcomes, patient quality of life, mortality, and hip-related complications – both within two years of the initial surgery. We are using minimization to ensure balance between intervention groups for the following factors: age, pre-fracture living, pre-fracture functional status, American Society for Anesthesiologists (ASA) Class, and centre number. Data analysts and the HEALTH Steering Committee are blinded to surgical allocation throughout the trial. Outcome analysis will be performed using a Chi-square test (or Fisher's exact test) and Cox proportional hazards modeling estimate. All results will be presented with 95% confidence intervals.

Ethics and Dissemination

The HEALTH trial has received local and McMaster University Research Ethics Board (REB) approval (REB#: 06-151). Results from the primary manuscript will be disseminated through publications in academic journals and presentations at relevant orthopaedic conferences.

Trial Registration

The HEALTH trial is registered with clinicaltrials.gov (NCT00556842).

STRENGTHS AND LIMITATIONS

Strengths

- This study has a large sample size of 1,434 patients in order to detect small but important differences in outcomes.
- We are utilizing an expertise-based randomized controlled trial design to help to eliminate differential performance and differential outcome assessments and reduce crossovers and ethical concerns associated with randomization.
- The study has stringent methodological safeguards against bias including: use of a centralized randomization system; blinding data analysts and the Steering Committee; standardization and documentation; use of strategies to limit loss to follow up; and adjudication of trial events by an independent Central Adjudication Committee.

Limitation

- Surgeons and patients cannot be blinded to the surgical arms, leaving the assessment of outcomes and decisions to re-operate vulnerable to bias.

INTRODUCTION

The number of hip fractures globally is expected to rise to over 6 million by the year 2050.[1, 2] Due to projected aging of the population, 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.[3-5] By the year 2040, the estimated annual health care costs associated with hip fractures will reach $9.8 billion in the United States and $650 million in Canada.[6] 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.[7] In the elderly, hip fractures are associated with a 30% mortality rate at 1 year post-injury and profound temporary,[8] and often permanent, impairment of independence and quality of life.[9, 10] Worldwide, 4.5 million people are disabled from hip fractures yearly with the number of persons living with disability expected to increase to 21 million in the next 40 years.[3, 5, 11] The disability adjusted life-years lost as a result of hip fractures ranks in the top 10 of all causes of global disability.[3]

Inconclusive Clinical Evidence

Femoral neck fractures may be either non-displaced (i.e., very little separation at the fracture site, about one third of femoral neck fractures) or displaced (i.e., greater separation at the fracture site, about two thirds of femoral neck fractures). Orthopaedic surgeons often treat non-displaced fractures with internal fixation and displaced fractures with arthroplasty, which is also known as joint replacement.

We conducted a comprehensive literature search to identify all studies investigating total hip arthroplasty (THA; involves replacing the femoral head and the acetabulum) compared to hemi-arthroplasty (HA; involves replacing the femoral head only) for displaced femoral neck fractures. We identified a recent meta-analysis of 14 studies (N=1,890 patients).[12] This meta-analysis demonstrated a lower risk of re-operation after THA compared with HA (relative risk 0.57, 95% CI 0.34 to 0.96); however, this effect was mainly driven by randomized controlled trials (RCTs) without concealed treatment allocation. THA consistently resulted in better hip function (Harris Hip Score, weighted mean difference 5.4, 95% CI 2.7 to 8.2) after follow-up intervals of 12 to 48 months.[12] We also identified two additional meta-analyses that provide comparisons of THA and HA.[13, 14] Liao et al pooled RCTs of THA (N=403 patients) versus HA (N=425 patients),[13] and found reductions in the risk of secondary procedures and wound infection with THA. Furthermore, Liao et al reported that the mobility rate in THA was better than in HA. Burgers et al performed a meta-analysis of eight RCTs (N=986 patients) that suggested similar rates of secondary procedures,[14] one year mortality, major complications, and minor complications with THA and HA, but large benefits in patient function with THA. Despite the benefits that THA confers regarding functional outcomes, secondary procedures, and infection rates, both meta-analyses reported higher hip dislocation rates with THA.

In a survey of 298 surgeons who were members of the Orthopaedic Trauma Association or affiliated with AO International, 94-96% of surgeons agreed that arthroplasty is the preferred treatment option in patients over 80 years of age with displaced femoral neck fractures.[15] In addition, 73% of surgeons surveyed preferred HA to THA.[15] In summary, current evidence suggests substantial benefits of THA over HA in decreased pain and improved function, but also increased rates of dislocation associated with THA, with similar rates of secondary procedures and mortality with the two procedures. Despite the apparent benefits of THA over HA, surgeons

more often prefer HA to treat displaced femoral neck fractures. Previous trials comparing these two approaches were limited by methodological issues, so the current trial aims to determine the effectiveness of THA compared to HA using a large sample size and high-quality methodology.

Study Objectives

Our primary objective is to assess the impact of THA versus HA on rates of unplanned secondary procedures at two years in individuals with displaced femoral neck fractures.

Secondary objectives are:

1. To examine the effect of THA versus HA 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 THA versus HA on mortality.
3. To evaluate the effect of THA versus HA 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 (e.g. pseudotumor), heterotopic ossification, abductor failure, implant wear and corrosion, osteolysis, neurovascular injury, decreased function, and pain.

METHODS AND ANALYSIS

Overview of Study Design

HEALTH is a multi-centre, concealed RCT of 1,434 elderly patients who have sustained a displaced femoral neck fracture. We are using minimization, a form of randomization, to determine patient allocation. Surgeons across North America, Europe, Australia, and Asia are participating. In conventional surgical hip fracture trials, all surgeons involved in the trial have performed both THA and HA based on the randomization process. HEALTH utilizes an expertise-based randomized trial design that allocates patients to surgeons with expertise in THA or HA (**Figure 1**). Based upon their expertise, surgeons perform either THA or HA. Surgeons who feel confident enough to perform both surgical strategies perform both THA and HA.

Patient Selection

Eligibility Criteria

The inclusion criteria are: 1) Adult men or women aged 50 years and older (with no upper age limit); 2) Fracture of the femoral neck confirmed with antero-posterior (AP) and lateral radiographs or computed tomography (CT) 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 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); and 10) Assurance that surgeons with expertise in both THA and HA are available to perform surgery.

The exclusion criteria are: 1) Patient not suitable for HA (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 (e.g. 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 (e.g. 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 two years); 7) Likely problems, in the judgment of the investigators, with maintaining follow-up (e.g. patients with no fixed address, report a plan to move out of town, or intellectually challenged patients without adequate family support); and 8) Patients whose fracture occurred as a result of an act of violence.

Patient Recruitment and Screening

All patients presenting to participating surgeons with a diagnosed femoral neck fracture amenable to arthroplasty are screened for participation in the HEALTH trial. Such patients are classified as: 1) Excluded (if they do not meet the eligibility criteria); 2) Missed (presumed eligible but missed due to error or staff availability); or 3) Included (eligible and randomized). Study personnel obtain informed consent from all eligible patients. If a patient lacks capacity and is deemed unable to consent, study personnel may obtain informed consent from the patient's legally authorized representative.

Randomization

We are ensuring concealment of allocation by using a centralized 24-hour computerized randomization system that will allow internet-based randomization. Patients are the unit of randomization. To protect against prognostic imbalance between groups, we are using minimization to ensure balance between intervention groups for several patient factors. The minimization approach takes into account each pre-identified prognostic variable and sums over the variables to allocate each patient to the treatment that will minimize the differences between groups for those prognostic variables. Unlike stratified randomization, minimization works toward minimizing the total imbalance for all factors together instead of considering mutually exclusive subgroups (strata).[16] Based on our international survey of surgeons,[15] and current evidence,[17] we are minimizing for the following prognostic factors: 1) Age (i.e., 50 to 80 years or greater than 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); and 5) Participating centre.

Study Interventions

Total Hip Arthroplasty

In the THA group, we are not including minimally invasive THA (i.e., 2 incision approaches) or hinged prostheses or capture cups. To optimize feasibility and applicability of results, we did not standardize the surgical approach including the use of cemented components, the implant manufacturer, or femoral head size. We are documenting the manufacturer, implant material, and bearing surface of the implant.

Hemi-Arthroplasty

Surgeons are to use modern implants for HA excluding non-modular, non-canal filling unipolar implants such as Moore's and Thompson's prostheses. We did not standardize the choice of modular unipolar versus bipolar HA nor whether implants are inserted with cement or with a press-fit design. We are documenting the manufacturer, implant material, and bearing surface of the implant.

Standardization of Procedures and Peri-Operative Care

To ensure similar peri-operative regimens, we recommend that participating centres standardize key aspects of pre- and post-operative care. For pre-operative care, we recommend standardization of the following: (1) Pre-operative antibiotic prophylaxis (e.g. cephalosporins or equivalent coverage); (2) Thromboprophylaxis (e.g. thromboembolic deterrent 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)); and (3) Medical consultation to optimize condition prior to surgery. For post-operative care, we recommend standardization of the following: (1) Antibiotic prophylaxis (e.g. 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 are weightbearing as tolerated, and then advanced according to the attending surgeon's best judgment; (4) 600 mg calcium by mouth daily and 1000 IU vitamin D per day (provided there are no contraindications) and further investigation and treatment of osteoporosis as recommended by a local osteoporosis expert/consultant; and (5) Appropriate nutritional assessment with administration of oral micronutrient feeds as needed. Due to a lack of evidence favouring a particular approach, we are recording but did not standardize the following: (1) Use of pre-operative traction; (2) Surgical delay; (3) Type of anesthetic (i.e., general or regional); and (4) Patient participation in physiotherapy and rehabilitation.

Study Outcomes

Primary Study Outcome

The primary outcome is any unplanned secondary procedure within 2 years of the initial hip 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**).

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

Specific unplanned secondary procedures include:	Classification of the reason for secondary procedures is as follows:
• Closed reduction of hip dislocation • Open reduction of hip dislocation • Open reduction of fracture • Soft tissue procedure	• Treat a peri-prosthetic fracture • Treat hip instability or dislocation • Treat infection – superficial • Treat infection – deep

• Insertion of antibiotic spacer • Full implant exchange • Partial implant exchange – stem only • Partial implant exchange - head only • Partial implant exchange - liner only • Partial implant exchange - head and liner • Partial implant exchange – acetabular component only • Partial implant exchange – acetabular component and head • Implant adjustment – re-orientation of the stem • Implant adjustment – re-orientation of the acetabulum component • Implant removal with no replacement • Excision heterotopic ossification • Supplementary fixation	• Treat wound necrosis • Treat another wound healing problem • Remove heterotopic ossification • Manage abductor failure • Manage another soft tissue problem (i.e. pseudotumor) • Correct implant failure –loosening or subsidence • Correct implant failure - breakage • Treat implant wear • Treat osteolysis • Treat implant corrosion • Improve function • Relieve pain

Secondary Study Outcomes

Secondary outcomes include: 1) Functional outcome and quality of life measured using self-administered and interview-administered questionnaires. 2) The effect of THA versus HA on mortality; 3) 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 (e.g. pseudotumor), heterotopic ossification, abductor failure, implant wear and corrosion, osteolysis, neurovascular injury, decreased function, or pain.

Functional outcome and quality of life are measured using self-administered and interview-administered questionnaires. Functional outcome questionnaires include a generic health status measurement instrument (SF-12),[18] a hip function and pain questionnaire (WOMAC),[19] a health outcome measure (EQ-5D),[20] and a functional mobility test (TUG).[21]

The SF-12 questionnaire 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). The instrument has been extensively validated and has demonstrated good construct validity, high internal consistency, and high test-retest reliability.[22] It is frequently used in orthopaedics for evaluating fracture outcomes.

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.[19] It is a valid,

reliable and responsive measure of outcome, and has been used in several studies involving a wide range of lower extremity conditions.[23]

The EQ-5D is a comprehensive, compact health status classification and health state preference system.[20] This questionnaire is widely used and has demonstrated validity and sensitivity in many populations.[20, 22] The EQ-5D is generalizable, as it is widely used in Europe, and will be useful for our definitive trial in which we will be including international sites.

The timed up and go test (TUG) involves observing the patient and documenting the time,[21] in seconds, it takes for the patient to rise from a standard arm chair, walk to a line on the floor 3 metres away, turn, return, ands sit down again. The TUG has been used in many clinical contexts including orthopaedics,[24] rheumatology,[25] and predicting geriatric falls.[26]

Adjudication of Study Events

The HEALTH Central Adjudication Committee (CAC) is comprised of five orthopaedic surgeons who specialize in hip surgery and have expertise in research methodology and experience with clinical trials. The CAC are reviewing: 1) Cases where fracture eligibility is in doubt; 2) Post-operative x-rays to assess the technical placement of prostheses; 3) All reported secondary procedures and fracture-related complications to determine if a secondary procedure and/or fracture-related complication meeting study criteria has occurred; and 4) Cases of mortality to confirm the cause of death. All centres submit digital x-rays to the HEALTH Methods Centre. We post all relevant patient records devoid of personal identifiers (i.e., case report forms and x-rays) on a specially designed, password-protected website for study adjudication. Adjudication occurs after patients have completed their two year follow-up. Any disagreements among the CAC members are resolved during conference calls. All decisions made by the Committee are final.

Study Follow Up

All patients are followed for a period of two years. At each follow up interval, patients' health status and outcomes are recorded. In addition, at the 2-year follow-up visit, the surgeon documents any secondary procedure that may be planned for the patient. **Figure 2** shows the schedule of events and assessments at each time point.

Our choice of a 2-year follow-up period is dictated by two factors. First, previous studies have reported that 75% of revision surgeries occur before 12 months for patients treated with arthroplasty for displaced femoral neck fractures.[27] Thus, we can expect that the majority of revision surgeries will occur within 2 years. Since increasing follow-up to beyond 2 years will yield little additional information on secondary procedure rates, efficient use of resources dictates a 2-year follow-up. Second, a full 2 years of follow-up will provide sufficient time to assess any potential gains in function and quality of life afforded by either surgical alternative.

Protecting Against Sources of Bias

Blinding

While surgeons, patients, and outcome assessors cannot be blinded to the surgical arms (i.e., THA or HA), data analysts and the Steering Committee will remain blinded throughout the trial. Secondary procedures, the primary outcome, are objective and lack of blinding introduces

minimal threats to validity. Additionally, the HEALTH trial design eliminates differential expertise bias by establishing a minimal threshold for experience, as well as ensuring that all surgeons performing either THA or HA are dedicated to and have sufficient expertise with the procedure.

Surgeon Expertise

Surgeons participating in the HEALTH trial are asked to meet both of the following two criteria for expertise for either THA or HA: 1) Perform at least 50 procedures (either THA or HA) in their career (including residency experience in which they assumed responsibility for the procedure), and 2) Perform at least 5 procedures per year. Surgeons who meet the threshold for both THA and HA will perform both procedures, if no overwhelming bias in favour of one procedure is evident. A surgeon is 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 the threshold expertise criteria and must be present in the operating room for the critical aspects of the procedure (**Table 2**). Our decision to set 50 procedures as the threshold for experience is based upon previous studies examining learning curves and respective outcomes in patients undergoing THA.[28-30] Our survey of surgeons who are members of the Orthopaedic Trauma Association (OTA) or European AO International trauma centres suggests that the threshold of HA is likely similar or slightly lower, given the perception of increased difficulty of THA.

Devereaux and colleagues have outlined the advantages of this trial design,[31] 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 over the other.
2. Differential performance, co-intervention, data collection, and outcome assessment are less likely than in conventional RCT.

With this approach, ethical concerns are reduced because all surgeries are conducted by surgeons with expertise and conviction concerning the procedures.[31]

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

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

Maximizing Patient Retention

Previous trials in hip fracture surgery have lost up to 50% of patients to follow-up.[15] To avoid this problem, the strategies outlined in **Figure 3** are used to minimize loss to follow-up. We have successfully used the majority of these strategies to maximize follow-up in other multi-centre studies. Key features of this strategy include: 1) excluding individuals who are likely to present problems with follow-up; 2) prior to hospital discharge, in addition to proving their own contact information, each patient provides the name and address of alternate contacts who are likely to be aware of the patient's whereabouts; 3) patients receive a reminder for their next follow up visit from the clinical research coordinator; and 4) follow-up visits coincide with standard fracture clinic visits. Additionally, patients can complete some study visits over the phone provided no radiographs are required.

Minimizing Co-Interventions and Contamination

Any patients who cross over from one treatment group to the other will be analyzed in the group to which they were allocated, maintaining the intention to treat approach of the analysis. Surgical co-interventions such as general, neurosurgical, or orthopaedic procedures performed in addition to the arthroscopy procedure, have the potential to confound outcomes. The standardization of key aspects of pre-operative and post-operative care, together with the expertise-based trial design will minimize the use of co-interventions in study patients. Clinical sites record the details of any major additional procedures performed, as well as the use of medications that affect bone, such as bisphosphonates, vitamin D, calcium, hormone replacement therapy, selective estrogen receptor modulators, calcitonin, and anabolic steroid therapy.

Maximizing Protocol Adherence

Given the inherent variability in practice patterns among orthopaedic surgeons, we believe it is important to ensure that surgeons adhere as closely as possible to the surgical management protocol. The feasibility of this large study involving multiple centres further depends upon minimal changes from current practice. Our study protocol closely follows currently accepted practice in the management of patients with femoral neck fractures. We therefore anticipate high compliance with our protocol.

Statistical Plan

Sample Size Determination

The choice of sample size is based upon a comparison of THA versus HA for the primary outcome (unplanned secondary procedures). 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**).

Table 3a: Sample Size Calculations Comparing Total Hip Arthroplasty (THA) and Hemi-

Arthroplasty (HA)

Studies included in a meta-analysis comparing THA with HA for the outcome of reoperation at one year

Study	THA Reoperation Rate	HA Reoperation Rate
van den Bekerom 2010 [32]	5/110 (4.5%)	1/136 (0.7%)
Baker 2006 [33]	4/36 (11.1%)	2/39 (5.1%)
Blomfeldt 2007 [34]	4/56 (7.1%)	3/57 (5.3%)
Keating 2006 [35]	6/63 (9.5%)	5/64 (7.8%)
Macaulay 2008 [36]	1/16 (6.25)	0/23 (0%)

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)

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.[37] 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 corresponding 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.

Table 3b: Sample Size Calculations Comparing Total Hip Arthroplasty (THA) and Hemi-Arthroplasty (HA)

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

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

RRR = Relative Risk Reduction

For the secondary outcomes, an important difference in SF-12 is considered to correspond to a moderate effect as reported by Cohen as well as a minimally important difference in the SF-12 as reported by Ware.[38, 39] 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,[40] 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.[41] In this study, at least 90 patients (45 per group) would be required to detect this difference (alpha level=0.05, beta=0.20, σ =15). Previous studies have found a standard deviation of 0.20 for the EQ-5D.[42] 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.

Primary Analyses
All outcome analyses will be performed by an intention to treat approach. To evaluate the effect of THA versus HA on time to unplanned 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); American Society for Anesthesiologists (ASA) Class (i.e., Class I/II or III/IV/V); and 5) Centre number. Results will be reported as hazard ratios with 95% confidence intervals. Kaplan-Meier curves will be constructed.

Secondary Analyses

A generalized linear model will estimate the effect of THA versus HA 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 (50 to 80 years or greater than 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); and 5) Participating centre.

Cox proportional hazards modeling will estimate the relative effect of THA versus HA 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.

Interim Analyses

The approach to interim analyses is guided by a desire to avoid spuriously inflated estimates of treatment effect.[43] 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. 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.

Data Management

The Case Report Forms (CRFs) are the primary data collection tool for the study. An Electronic Data Capture system (iDataFax) is being used to submit data to the Methods Centre located at McMaster University. Upon receipt of the data, the personnel at the Methods Centre make a visual check of the data and they query all missing data, implausible data, and inconsistencies.

Sensitivity Analyses

We will perform some sensitivity analyses to assess the robustness of the primary results. First, we will perform a competing risk analysis using Fine and Gray method to account for death as a competing risk.[44] Second, we will use the random-effects analysis with a centre as a random-effect to account for the possibility of the centre effect or clustering within a centre. Lastly, based on the pilot results we anticipate some cross-overs during the trial—we will monitor these and perform some sensitivity analysis to assess their impact. All analyses will be performed using SAS 9.2 (Cary, NC).

Missing Data

Patients who are lost or withdrawn from the study prior to full 24 month follow-up will be censored at their last visit where evaluation of the primary endpoint was completed.

Data Monitoring Committee

The purpose of the Data Monitoring Committee (DMC) is to advise the HEALTH Investigators regarding the continuing safety of study participants. The DMC consists of the Chair, who is an orthopaedic surgeon, one biostatistician, and two additional orthopaedic surgeons. All members are independent of the trial investigators, and have neither financial nor scientific conflicts of interest with the trial. Further details regarding the DMC can be found in the DMC Charter, available from the corresponding author.

ETHICAL CONSIDERATIONS

All patients included in this study will sign a consent form that describes this study and provides sufficient information for patients to make an informed decision about their participation. All participating centres will submit the consent form with the protocol for review and approval by their local research ethics board (REB) or institutional review board (IRB) for the study. Centres will obtain written consent from every patient, using the REB/IRB-approved consent form, before that patient undergoes any study procedure. Any amendments to the study protocol which may affect the conduct of the study, or the potential safety of or benefits to patients will require a formal amendment to the protocol requiring approval by McMaster University's REB and local research ethics boards for clinical sites. Any protocol amendments will be communicated to investigators, REB/IRB, trial participants, and trial registries as necessary.

Information about study patients will be kept confidential and will be managed in accordance with the following rules: (1) All study-related information will be stored securely at the clinical site; (2) All study patient information will be stored in locked file cabinets and accessible only to study personnel; (3) All CRFs will be identified only by a coded patient number and initials; (4) All records that contain patient names, or other identifying information, will be stored separately from the study records that are identified only by the coded patient number and initials; and (5) All local databases will be password protected.

DISSEMINATION

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

Only the Methods Centre will have access to the full trial dataset. Data for the primary publication will be analyzed exclusively by the Methods Centre. Requests for access to the full trial dataset for secondary publications are encouraged and can be initiated through a written request to Methods Centre personnel.

DISCUSSION

Previous orthopaedic trials have addressed the effect of THA versus HA on patient outcomes; however, the trials conducted to date are limited by small sample sizes, lack of concealed randomization, differential expertise biases,[13] and most were single centre initiatives that lacked sufficient power to inform surgical practice. Orthopaedic surgeons appear to currently favor HA, although current evidence suggests superior patient-important outcomes with THA.[14, 31] The HEALTH trial will aim to resolve these controversies by establishing the

effectiveness of each method of arthroplasty. This will have important clinical implications as each treatment is easily applicable and already in use in orthopaedic practice.

The HEALTH trial will address and overcome many of the limitations of previous orthopaedic hip fracture trials. Firstly, the study sample size of 1,434 patients is sufficient to detect small, but important differences in outcomes, and will ensure that our study objectives are met. Secondly, using an expertise-based RCT has many advantages over traditional orthopaedic hip studies, including eliminating differential performance and differential outcome assessment and reducing the number of crossovers and ethical concerns associated with randomization.[13] Furthermore, the HEALTH trial has stringent methodological safeguards against bias including: the use of a centralized system to randomize patients; blinding data analysts and the Steering Committee; standardization and documentation of pre-operative care, peri-operative care and post-operative care; the use of strategies to limit loss to follow up; and adjudication of trial events by an independent Central Adjudication Committee.

A key limitation of the HEALTH trial is that surgeons and patients cannot be blinded to the surgical arms. This leaves the assessment of outcomes and decisions to re-operate vulnerable to bias. We have limited this bias by using an objective primary outcome (unplanned secondary procedures) and by centrally adjudicating all primary outcome events using a group of independent orthopaedic surgeons.

The results of the HEALTH trial will be an important contribution to orthopaedic surgical literature and likely lead to changes in orthopaedic practice. Identifying the optimal approach to arthroplasty has the potential to improve the lives of hundreds of thousands of patients and to reduce the economic burden associated with hip fractures. If this trial shows that one approach is superior to the other, it will revolutionize the treatment of hip fractures globally, and may potentially lead to the establishment of new clinical guidelines for treatment of displaced femoral neck fractures. In addition to the clinical impact, the HEALTH trial also has the potential to impact orthopaedic trial conduct. With this trial we will build collaborative relationships among countries and between clinical centres. This trial will also contribute to challenging the dogma that surgical trials are doomed to small single centre initiatives.

REFERENCES

1. Cooper C, Campion G, Melton LJ, 3rd. Hip fractures in the elderly: a world-wide projection. *Osteoporos Int* 1992;2:285–9.
2. Dhanwal DK, Dennison EM, Harvey NC, et al. Epidemiology of hip fracture: worldwide geographic variation. *Indian J Orthop* 2011;45(1):15–22.
3. Johnell O, Kanis JA. An estimate of the worldwide prevalence, mortality and disability associated with hip fracture. *Osteoporos Int* 2004;15:897–902.
4. Iorio R, Schwartz B, Macaulay W, et al. Surgical treatment of displaced femoral neck fractures in the elderly: a survey of the American association of hip and knee surgeons. *Arthrop* 2006;21(8):1124-33.
5. Cummings SR, Rubin SM, Black D. The future of hip fractures in the United States. Numbers, costs, and potential effects of postmenopausal estrogen. *Clin Orthop Relat Res* 1990;252:163–6.
6. Papadimitropoulos EA, Coyte PC, Josse RG, et al. Current and projected rates of hip fracture in Canada. *CMAJ* 1997;157:1357-63.
7. AAOS urges hip fracture reform. American Academy of Orthopaedic Surgeons Bulletin 1999;47.
8. Moran CG, Wenn RT, Sikand M, et al. Early mortality after hip fracture: is delay before surgery important? *J Bone Joint Surg* 2005;87:483-89.
9. Jongjit J, Komsopapong L, Songjakkaew P, et al. Health-related quality of life after hip fracture in the elderly community-dwelling. *Southeast Asian J Trop Med Public Health* 2003;34:670-4.
10. Carrière G. Hip fracture outcomes in the household population. *Health Rep* 2007;18(4):37-42.
11. Cooper C, Campion G, Melton LJ. Hip fractures in the elderly: a world-wide projection. *Osteoporos Int* 1992;2:285–9.
12. Hopley C, Stengel D, Ekkernkamp A, et al. Primary total hip arthroplasty versus hemiarthroplasty for displaced intracapsular hip fractures in older patients: systematic review. *BMJ* 2010;340:c2332.
13. Liao L, Zhao Jm, Su W, et al. A meta-analysis of total hip arthroplasty and hemiarthroplasty outcomes for displaced femoral neck fractures. *Arch Orthop Trauma Surg* 2012;132(7):1021-9.
14. Burgers PTPW, Van Geene AR, Van den Bekerom MPJ, et al. Total hip arthroplasty versus hemiarthroplasty for displaced femoral neck fractures in the healthy elderly: a meta-analysis and systematic review of randomized trials. *Int Orthop* 2012;36:1549-60.
15. Bhandari M, Devereaux PJ, Tornetta P 3rd, et al. Operative management of displaced femoral neck fractures in elderly patients. An international survey. J Bone Joint Surg Am 2005;87:2122-30.
16. Pandis N. Randomization. Part 2: Minimization. *Am J Orthod Dentofacial Orthop* 2011;140(6):902-4.
17. Gillespie WJ. Extracts from "clinical evidence": hip fracture. *BMJ* 2001;322:968-75.
18. McHorney CA, Ware JE Jr, Rogers W, et al. The validity and relative precision of MOS short- and long-form health status scales and Dartmouth COOP charts. Results from the medical outcomes study. *Med Care* 1992;30(5 suppl):MS253-65.
19. Bellamy N, Buchanan WW, Goldsmith CH, et al. Validation of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol* 1988;15:1833-40.

20. Brooks R, Rabin RE, de Charro F, (Eds). The Measurement and Valuation of Health Status Using EQ-5D: A European Perspective. Dordrecht, The Netherlands: Kulwer Academic Publishers 2003.
21. Podsiadlo D, Richardson S. The timed 'up and go' test: a test of basic functional mobility for frail elderly persons. *J of Am Geri Soc* 1991;39(2):142-8.
22. Ware JE, Kosinski M, Keller SD. A 12-item short-form health survey: construction of scales and preliminary tests of reliability and validity. *Med Care* 1996;34:220-33.
23. Dattani R, Slobogean GP, O'Brien PJ, et al. Psychometric analysis of measuring functional outcomes in tibial plateau fractures using the Short Form 36 (SF-36), Short Musculoskeletal Function Assessment (SMFA) and the Western Ontario McMaster Osteoarthritis (WOMAC) questionnaires. *Injury* 2013;44(6):825-9.
24. Laflamme GY, Rouleau DM, Leduc S, et al. The Timed Up and Go test is an early predictor of functional outcome after hemiarthroplasty for femoral neck fracture. J Bone Joint Surg Am. 2012;94(13):1175-9.
25. McMeeken J, Stillman B, Story I, et al. The effects of knee extensor and flexor muscle training on the timed-up-and-go test in individuals with rheumatoid arthritis. *Physiother Res Int* 1999;4(1):55-67.
26. Shumway-Cook A, Brauer S, Woollacott M. Predicting the probability for falls in community-dwelling older adults using the Timed Up & Go Test. *Phys Ther* 2000;80(9):896-903.
27. Ravikumar KJ, Marsh G. Internal fixation versus hemiarthroplasty versus total hip arthroplasty for displaced subcapital fractures of femur -13 year results of a prospective randomised study. *Injury* 2000;31:793-7.
28. Callaghan JJ, Heekin RD, Savory CG, et al. Evaluation of the learning curve associated with uncemented primary porous-coated anatomic total hip arthroplasty. *Clin Orthop Relat Res* 1992;282:132-44.
29. Ellinor N, Lindelof N, Rosendahl E, et al. Prognostic validity of the Timed Up-and-Go test, staff's global judgement and fall history in evaluating fall risk in residential care facilities. *Age Ageing* 2008;37:442-8.
30. Katz JN, Losina E, Barrett J, et al. Association between hospital and surgeon procedure volume and outcomes of total hip replacement in the United States medicare population. *J Bone Joint Surg Am* 2001;83-A(11):1622-9.
31. Devereaux PJ, Bhandari M, Clarke M, et al. Need for expertise based randomised controlled trials. BMJ 2005;330:88-91.
32. van den Bekerom MP, Hilverdink EF, Sierevelt IN, et al. A comparison of hemiarthroplasty with total hip replacement for displaced intracapsular fracture of the femoral neck: a randomised controlled multicentre trial in patients aged 70 years and over. J Bone Joint Surg Br. 2010;92(10):1422-8.
33. Baker RP, Squires B, Gargan MF, et al. Total hip arthroplasty and hemiarthroplasty in mobile, independent patients with a displaced intracapsular fracture of the femoral neck. A randomized, controlled trial. J Bone Joint Surg Am. 2006;88(12):2583-9.
34. Blomfeldt R, Törnkvist H, Eriksson K, et al. A randomised controlled trial comparing bipolar hemiarthroplasty with total hip replacement for displaced intracapsular fractures of the femoral neck in elderly patients. J Bone Joint Surg Br. 2007;89(2):160-5.

35. Keating JF, Grant A, Masson M, et al. Displaced intracapsular hip fractures in fit, older people: a randomised comparison of reduction and fixation, bipolar hemiarthroplasty and total hip arthroplasty. *Health Technol Assess* 2005:9;1-65.
36. Macaulay W, Nellans KW, Garvin KL, et al. Prospective randomized clinical trial comparing hemiarthroplasty to total hip arthroplasty in the treatment of displaced femoral neck fractures. J Arthroplasty. 2008;23(6 Suppl 1):2-8.
37. Collett D. Modelling Survival Data in Medical Research. London, UK: Chapman & Hall 1994.
38. Cohen J. Statistical Power Analysis For The Behavioral Sciences. 2nd editions. Hillsdale, NJ: Lawrence Erlbaum Associates 1988.
39. Ware JE, Sherbourne CD. The MOS 36-item short form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30:473-83.
40. Jaglal S, Lakhani Z, Schatzker J. Reliability, validity, and responsiveness of the lower extremity measure for patients with a hip fracture. *J Bone Joint Surg Am* 2000;82:955-62.
41. Tubach F, Ravaud P, Baron G, et al. Evaluation of clinically relevant changes in patient reported outcomes in knee and hip osteoarthritis: The minimal clinically important improvement. *Ann Rheum Dis* 2005;64:29-33.
42. Tidermark J, Ponzer S, Svensson O, et al. Internal fixation compared with total hip replacement for displaced femoral neck fractures in the elderly: a randomised, controlled trial. *J Bone Joint Surg Br* 2003;85:380–8.
43. Montori VM, Devereaux PJ, Adhikari NK, et al. Stopping randomized clinical trials early for benefit: a protocol of the study of trial policy of interim truncation-2 (STOPIT-2). *Trials* 2009;10:49.
44. Fine J, Gray R. A proportional hazards model for the sub-distribution of a competing risk. *J Am Stat Assoc* 1999;94:496-509.

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COMPETING INTEREST STATEMENT

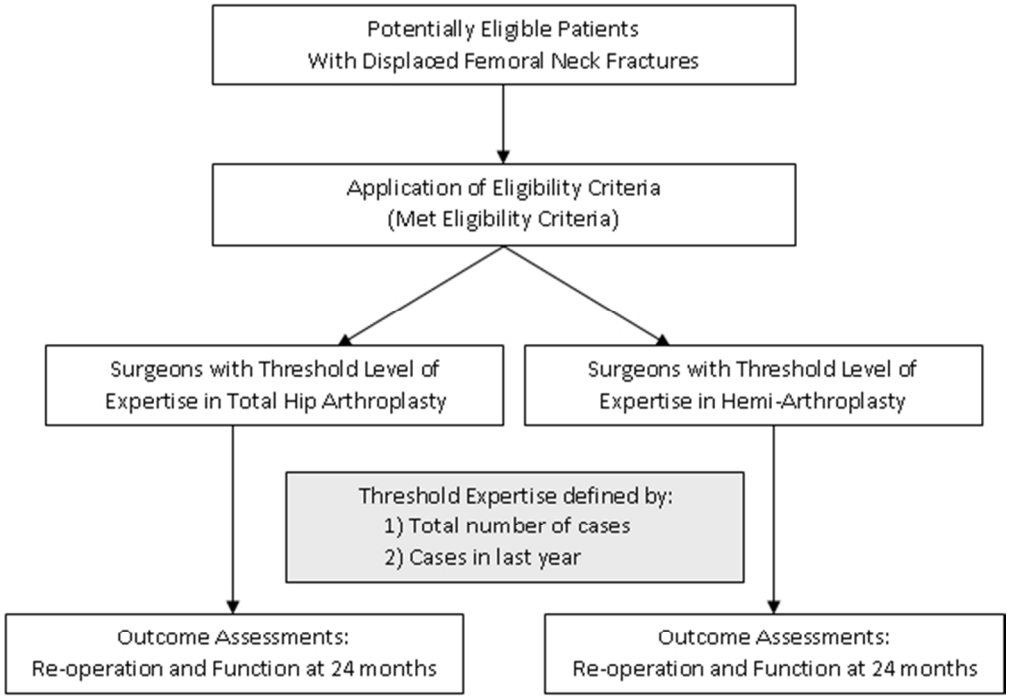
The authors have no competing interests to report.

FIGURE LEGEND

Figure 1: Expertise-Based Randomized Controlled Trial
An expertise-based randomized controlled trial design randomizes participants to surgeons with expertise in surgery A or to surgeons with expertise in surgery B.

Figure 2: Schedule of Events
** Complete forms when and/or if applicable*

Figure 3: Strategies to Enhance Follow-Up Rates



Expertise-Based Randomized Controlled Trial
An expertise-based randomized controlled trial design randomizes participants to surgeons with expertise in surgery A or to surgeons with expertise in surgery B.
158x135mm (96 x 96 DPI)

Radiographs & Event Forms	Pre-Surgery			Surgery	Post Surgery								
	Screening	Enrollment	Baseline	(Day 0)	≤ 48 hrs Post Surgery	Discharge	1 wk	10 wk	6 mo	9 mo	12 mo	18 mo	24 mo
Patient Contact		•			•	•	•	•	•	•	•	•	•
Radiographs			•		•			•			•		•
Screening	•												
Informed Consent		•											
Randomization		•											
Baseline			•										
Surgical Report				•									
Post-Op Care					•								
Clinic or Telephone Follow-Up							•	•	•	•	•	•	•
Secondary Procedure					*		*	*	*	*	*	*	*
Adverse Event				*	*		*	*	*	*	*	*	*
Timed Up and Go								•	•		•		•
SF-12							•	•	•	•	•	•	•
WOMAC							•	•	•	•	•	•	•
EQ-5D							•	•	•	•	•	•	•
Missed Follow-Up						*	*	*	*	*	*	*	
Early W/D						*	*	*	*	*	*	*	*

Schedule of Events
* Complete forms when and/or if applicable

Before the study begins	At screening	At baseline	During the study	For patients who are difficult to contact
• Create a study identity that includes a logo on all study documents • Train research personnel in maintaining participant confidentiality • Ensure all study personnel are aware of study procedures	• Exclude participants who are likely to be difficult to follow for the duration of the trial (e.g. no fixed addresss, patients with dementia and no family support) • Be explicit about follow up procedures including when to expect contact from study staff, how often, and what type of contact (in person, email, phone etc.)	• Collect several personal contacts including friends or family members to assist with locating patients later • Ensure informed consent is conducted in an appropriate manner, including using examples and explanations that are accessible to a lay audience	• Provide participants with a choice of email, phone, and/or in-clinic visits when appropriate (i.e. when no radiographs are required) • Be flexible on scheduling in-clinic visits • Ensure participants can easily contact study personnel by providing them with contact informatio nthat is easy to access • Routinely verify that the participant's contact information is up to date	• Try previously disconnected phone numbers • Search online or in telephone books for updated contact information • Search the hospital's database for hospital admissions • Try to contact participants form a different phone number or at a different time of day • Hold regular staff meetings to brainstorm creative ways to locate participants who are dificult to contact

Strategies to Enhance Follow-Up Rates

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	1-22
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	20
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	20-22
	5b	Name and contact information for the trial sponsor	N/A
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	20
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	14-15, 20-22

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	4-5
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4-5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5-6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	11
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9-10

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11-13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	11
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6-7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6-7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6-7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9-10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8-9
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	14
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12-14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14-15
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	14
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	7-9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	15

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
	31b	Authorship eligibility guidelines and any intended use of professional writers	20
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Hip Fracture Evaluation with ALternatives of Total Hip Arthroplasty versus Hemi-Arthroplasty (HEALTH): Protocol for a Multi-Centre Randomized Trial

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Hip Fracture Evaluation with Alternatives of Total Hip Arthroplasty versus Hemi-Arthroplasty (HEALTH): Protocol for a Multi-Centre Randomized Trial

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ABSTRACT

Introduction

Hip fractures are a leading cause of mortality and disability worldwide and the number of hip fractures is expected to rise to over 6 million per year by 2050. The optimal approach for the surgical management of displaced femoral neck fractures remains unknown. Current evidence suggests the use of arthroplasty; however, there is lack of evidence regarding whether patients with displaced femoral neck fractures experience better outcomes with total hip arthroplasty (THA) or hemi-arthroplasty (HA). The HEALTH trial compares outcomes following THA versus HA in patients 50 years of age or older with displaced femoral neck fractures.

Methods and Analysis

HEALTH is a multi-centre, randomized controlled trial where 1,434 patients 50 years of age or older with displaced femoral neck fractures from international sites, are randomized to receive either THA or HA. Exclusion criteria include associated major injuries of the lower extremity, hip infection(s) and a history of frank dementia. The primary outcome is unplanned secondary procedures and the secondary outcomes include functional outcomes, patient quality of life, mortality, and hip-related complications – both within two years of the initial surgery. We are using minimization to ensure balance between intervention groups for the following factors: age, pre-fracture living, pre-fracture functional status, American Society for Anesthesiologists (ASA) Class, and centre number. Data analysts and the HEALTH Steering Committee are blinded to surgical allocation throughout the trial. Outcome analysis will be performed using a Chi-square test (or Fisher's exact test) and Cox proportional hazards modeling estimate. All results will be presented with 95% confidence intervals.

Ethics and Dissemination

The HEALTH trial has received local and McMaster University Research Ethics Board (REB) approval (REB#: 06-151). Results from the primary manuscript will be disseminated through publications in academic journals and presentations at relevant orthopaedic conferences.

Trial Registration

The HEALTH trial is registered with clinicaltrials.gov (NCT00556842).

STRENGTHS AND LIMITATIONS

Strengths

- This study has a large sample size of 1,434 patients in order to detect small but important differences in outcomes.
- We are utilizing an expertise-based randomized controlled trial design to help to eliminate differential performance and differential outcome assessments and reduce crossovers and ethical concerns associated with randomization.
- The study has stringent methodological safeguards against bias including: use of a centralized randomization system; blinding data analysts and the Steering Committee; standardization and documentation; use of strategies to limit loss to follow up; and adjudication of trial events by an independent Central Adjudication Committee.

Limitation

- Surgeons and patients cannot be blinded to the surgical arms, leaving the assessment of outcomes and decisions to re-operate vulnerable to bias.
- We do not allow family members and friends to answer questionnaires on behalf of cognitively impaired patients, so some secondary outcomes will only apply to patients who are not cognitively impaired.
- The two year follow up limits the study to shorter-term outcomes.

INTRODUCTION

The number of hip fractures globally is expected to rise to over 6 million by the year 2050.[1, 2] Due to projected aging of the population, 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.[3-5] By the year 2040, the estimated annual health care costs associated with hip fractures will reach $9.8 billion in the United States and $650 million in Canada.[6] 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.[7] In the elderly, hip fractures are associated with a 30% mortality rate at 1 year post-injury and profound temporary,[8] and often permanent, impairment of independence and quality of life.[9, 10] Worldwide, 4.5 million people are disabled from hip fractures yearly with the number of persons living with disability expected to increase to 21 million in the next 40 years.[3, 5, 11] The disability adjusted life-years lost as a result of hip fractures ranks in the top 10 of all causes of global disability.[3]

Inconclusive Clinical Evidence

Femoral neck fractures may be either non-displaced (i.e., very little separation at the fracture site, about one third of femoral neck fractures) or displaced (i.e., greater separation at the fracture site, about two thirds of femoral neck fractures). Orthopaedic surgeons often treat non-displaced fractures with internal fixation and displaced fractures with arthroplasty, which is also known as joint replacement.

We conducted a comprehensive literature search to identify all studies investigating total hip arthroplasty (THA; involves replacing the femoral head and the acetabulum) compared to hemi-arthroplasty (HA; involves replacing the femoral head only) for displaced femoral neck fractures. We identified a recent meta-analysis of 14 studies (N=1,890 patients).[12] This meta-analysis demonstrated a lower risk of re-operation after THA compared with HA (relative risk 0.57, 95% CI 0.34 to 0.96); however, this effect was mainly driven by randomized controlled trials (RCTs) without concealed treatment allocation. THA consistently resulted in better hip function (Harris Hip Score, weighted mean difference 5.4, 95% CI 2.7 to 8.2) after follow-up intervals of 12 to 48 months.[12] We also identified two additional meta-analyses that provide comparisons of THA and HA.[13, 14] Liao et al pooled RCTs of THA (N=403 patients) versus HA (N=425 patients),[13] and found reductions in the risk of secondary procedures and wound infection with THA. Furthermore, Liao et al reported that the mobility rate in THA was better than in HA. Burgers et al performed a meta-analysis of eight RCTs (N=986 patients) that suggested similar rates of secondary procedures,[14] one year mortality, major complications, and minor complications with THA and HA, but large benefits in patient function with THA. Despite the benefits that THA confers regarding functional outcomes, secondary procedures, and infection rates, both meta-analyses reported higher hip dislocation rates with THA.

In a survey of 298 surgeons who were members of the Orthopaedic Trauma Association or affiliated with AO International, 94-96% of surgeons agreed that arthroplasty is the preferred treatment option in patients over 80 years of age with displaced femoral neck fractures.[15] In addition, 73% of surgeons surveyed preferred HA to THA.[15] In summary, current evidence suggests substantial benefits of THA over HA in decreased pain and improved function, but also increased rates of dislocation associated with THA, with similar rates of secondary procedures and mortality with the two procedures. Despite the apparent benefits of THA over HA, surgeons

more often prefer HA to treat displaced femoral neck fractures. Previous trials comparing these two approaches were limited by methodological issues, so the current trial aims to determine the effectiveness of THA compared to HA using a large sample size and high-quality methodology.

Study Objectives

Our primary objective is to assess the impact of THA versus HA on rates of unplanned secondary procedures at two years in individuals with displaced femoral neck fractures.

Secondary objectives are:

1. To examine the effect of THA versus HA 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 THA versus HA on mortality.
3. To evaluate the effect of THA versus HA 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 (e.g. pseudotumor), heterotopic ossification, abductor failure, implant wear and corrosion, osteolysis, neurovascular injury, decreased function, and pain.

METHODS AND ANALYSIS

Overview of Study Design

HEALTH is a multi-centre, concealed RCT of 1,434 elderly patients who have sustained a displaced femoral neck fracture. We are using minimization, a form of randomization, to determine patient allocation. Surgeons across North America, Europe, Australia, and Asia are participating. In conventional surgical hip fracture trials, all surgeons involved in the trial have performed both THA and HA based on the randomization process. HEALTH utilizes an expertise-based randomized trial design that allocates patients to surgeons with expertise in THA or HA (**Figure 1**). Based upon their expertise, surgeons perform either THA or HA. Surgeons who feel confident enough to perform both surgical strategies perform both THA and HA.

Patient Selection

Eligibility Criteria

The inclusion criteria are: 1) Adult men or women aged 50 years and older (with no upper age limit); 2) Fracture of the femoral neck confirmed with antero-posterior (AP) and lateral radiographs or computed tomography (CT) 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 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); and 10) Assurance that surgeons with expertise in both THA and HA are available to perform surgery.

The exclusion criteria are: 1) Patient not suitable for HA (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 (e.g. 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 (e.g. 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 two years); 7) Likely problems, in the judgment of the investigators, with maintaining follow-up (e.g. patients with no fixed address, report a plan to move out of town, alcohol abuse issues, or intellectually challenged patients without adequate family support); and 8) Patients whose fracture occurred as a result of an act of violence.

Patient Recruitment and Screening

The first patient was randomized into the vanguard phase of this trial on 21 January 2009. After a brief pause in enrollment between the vanguard and definitive phase, the first definitive patient was randomized on 8 October 2013. Enrollment is ongoing at the time pf publication and is expected to be completed by December 2016. All patients presenting to participating surgeons with a diagnosed femoral neck fracture amenable to arthroplasty are screened for participation in the HEALTH trial. Such patients are classified as: 1) Excluded (if they do not meet the eligibility criteria); 2) Missed (presumed eligible but missed due to error or staff availability); or 3) Included (eligible and randomized). Study personnel obtain informed consent from all eligible patients. If a patient lacks capacity and is deemed unable to consent, study personnel may obtain informed consent from the patient's legally authorized representative and assent from the patient.

Randomization

We are ensuring concealment of allocation by using a centralized 24-hour computerized randomization system that will allow internet-based randomization. Patients are the unit of randomization. To protect against prognostic imbalance between groups, we are using minimization to ensure balance between intervention groups for several patient factors. The minimization approach takes into account each pre-identified prognostic variable and sums over the variables to allocate each patient to the treatment that will minimize the differences between groups for those prognostic variables. Unlike stratified randomization, minimization works toward minimizing the total imbalance for all factors together instead of considering mutually exclusive subgroups (strata).[16] Based on our international survey of surgeons,[15] and current evidence,[17] we are minimizing for the following prognostic factors: 1) Age (i.e., 50 to 80 years or greater than 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); and 5) Participating centre.

Study Interventions

Total Hip Arthroplasty

In the THA group, we are not including minimally invasive THA (i.e., 2 incision approaches) or hinged prostheses or capture cups. To optimize feasibility and applicability of results, we did not standardize the surgical approach including the use of cemented components, the implant manufacturer, or femoral head size. We are documenting the manufacturer, implant material, and bearing surface of the implant.

Hemi-Arthroplasty

Surgeons are to use modern implants for HA excluding non-modular, non-canal filling unipolar implants such as Moore's and Thompson's prostheses. We did not standardize the choice of modular unipolar versus bipolar HA nor whether implants are inserted with cement or with a press-fit design. We are documenting the manufacturer, implant material, and bearing surface of the implant.

Standardization of Procedures and Peri-Operative Care

To ensure similar peri-operative regimens, we recommend that participating centres standardize key aspects of pre- and post-operative care. For pre-operative care, we recommend standardization of the following: (1) Pre-operative antibiotic prophylaxis (e.g. cephalosporins or equivalent coverage); (2) Thromboprophylaxis (e.g. oral anticoagulation drugs, thromboembolic deterrent 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)); and (3) Medical consultation to optimize condition prior to surgery. For post-operative care, we recommend standardization of the following: (1) Antibiotic prophylaxis (e.g. 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 are weightbearing as tolerated, and then advanced according to the attending surgeon's best judgment; (4) 600 mg calcium by mouth daily and 1000 IU vitamin D per day (provided there are no contraindications) and further investigation and treatment of osteoporosis as recommended by a local osteoporosis expert/consultant; and (5) Appropriate nutritional assessment with administration of oral micronutrient feeds as needed. Due to a lack of evidence favouring a particular approach, we are recording but did not standardize the following: (1) Use of pre-operative traction; (2) Surgical delay; (3) Type of anesthetic (i.e., general or regional); and (4) Patient participation in physiotherapy and rehabilitation.

Study Outcomes

Primary Study Outcome

The primary outcome is any unplanned secondary procedure within 2 years of the initial hip 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**).

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

Specific unplanned secondary procedures	Classification of the reason for secondary

include:	procedures is as follows:
• Closed reduction of hip dislocation • Open reduction of hip dislocation • Open reduction of fracture • Soft tissue procedure • Insertion of antibiotic spacer • Full implant exchange • Partial implant exchange – stem only • Partial implant exchange - head only • Partial implant exchange - liner only • Partial implant exchange - head and liner • Partial implant exchange – acetabular component only • Partial implant exchange – acetabular component and head • Implant adjustment – re-orientation of the stem • Implant adjustment – re-orientation of the acetabulum component • Implant removal with no replacement • Excision heterotopic ossification • Supplementary fixation	• Treat a peri-prosthetic fracture • Treat hip instability or dislocation • Treat infection – superficial • Treat infection – deep • Treat wound necrosis • Treat another wound healing problem • Remove heterotopic ossification • Manage abductor failure • Manage another soft tissue problem (i.e. pseudotumor) • Correct implant failure –loosening or subsidence • Correct implant failure - breakage • Treat implant wear • Treat osteolysis • Treat implant corrosion • Improve function • Relieve pain

Secondary Study Outcomes

Secondary outcomes include: 1) Functional outcome and quality of life measured using self-administered and interview-administered questionnaires. 2) The effect of THA versus HA on mortality; 3) 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 (e.g. pseudotumor), heterotopic ossification, abductor failure, implant wear and corrosion, osteolysis, neurovascular injury, decreased function, or pain.

Functional outcome and quality of life are measured using self-administered and interview-administered questionnaires. Functional outcome questionnaires include a generic health status measurement instrument (SF-12),[18] a hip function and pain questionnaire (WOMAC),[19] a health outcome measure (EQ-5D),[20] and a functional mobility test (TUG).[21]

The SF-12 questionnaire 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). The instrument has been extensively validated and has demonstrated good construct validity, high internal

consistency, and high test-retest reliability.[22] It is frequently used in orthopaedics for evaluating fracture outcomes.

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.[19] It is a valid, reliable and responsive measure of outcome, and has been used in several studies involving a wide range of lower extremity conditions.[23]

The EQ-5D is a comprehensive, compact health status classification and health state preference system.[20] This questionnaire is widely used and has demonstrated validity and sensitivity in many populations.[20, 22] The EQ-5D is generalizable, as it is widely used in Europe, and will be useful for our definitive trial in which we will be including international sites.

The timed up and go test (TUG) involves observing the patient and documenting the time,[21] in seconds, it takes for the patient to rise from a standard arm chair, walk to a line on the floor 3 metres away, turn, return, ands sit down again. The TUG has been used in many clinical contexts including orthopaedics,[24] rheumatology,[25] and predicting geriatric falls.[26]

Adjudication of Study Events

The HEALTH Central Adjudication Committee (CAC) is comprised of five orthopaedic surgeons who specialize in hip surgery and have expertise in research methodology and experience with clinical trials. The CAC are reviewing: 1) Cases where fracture eligibility is in doubt; 2) Post-operative x-rays to assess the technical placement of prostheses; 3) All reported secondary procedures and fracture-related complications to determine if a secondary procedure and/or fracture-related complication meeting study criteria has occurred; and 4) Cases of mortality to confirm the cause of death. All centres submit digital x-rays to the HEALTH Methods Centre. We post all relevant patient records devoid of personal identifiers (i.e., case report forms and x-rays) on a specially designed, password-protected website for study adjudication. Adjudication occurs after patients have completed their two year follow-up. Any disagreements among the CAC members are resolved during conference calls. All decisions made by the Committee are final.

Study Follow Up

All patients are followed for a period of two years. At each follow up interval, patients' health status and outcomes are recorded. In addition, at the 2-year follow-up visit, the surgeon documents any secondary procedure that may be planned for the patient. **Figure 2** shows the schedule of events and assessments at each time point.

Our choice of a 2-year follow-up period is dictated by two factors. First, previous studies have reported that 75% of revision surgeries occur before 12 months for patients treated with arthroplasty for displaced femoral neck fractures.[27] Thus, we can expect that the majority of revision surgeries will occur within 2 years. Since increasing follow-up to beyond 2 years will yield little additional information on secondary procedure rates, efficient use of resources dictates a 2-year follow-up. Second, a full 2 years of follow-up will provide sufficient time to assess any potential gains in function and quality of life afforded by either surgical alternative.

Protecting Against Sources of Bias

Blinding

While surgeons, patients, and outcome assessors cannot be blinded to the surgical arms (i.e., THA or HA), data analysts and the Steering Committee will remain blinded throughout the trial. Secondary procedures, the primary outcome, are objective and lack of blinding introduces minimal threats to validity. Additionally, the HEALTH trial design eliminates differential expertise bias by establishing a minimal threshold for experience, as well as ensuring that all surgeons performing either THA or HA are dedicated to and have sufficient expertise with the procedure.

Surgeon Expertise

Surgeons participating in the HEALTH trial are asked to meet both of the following two criteria for expertise for either THA or HA: 1) Perform at least 50 procedures (either THA or HA) in their career (including residency experience in which they assumed responsibility for the procedure), and 2) Perform at least 5 procedures per year. Surgeons who meet the threshold for both THA and HA will perform both procedures, if no overwhelming bias in favour of one procedure is evident. A surgeon is 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 the threshold expertise criteria and must be present in the operating room for the critical aspects of the procedure (**Table 2**). Our decision to set 50 procedures as the threshold for experience is based upon previous studies examining learning curves and respective outcomes in patients undergoing THA.[28-30] Our survey of surgeons who are members of the Orthopaedic Trauma Association (OTA) or European AO International trauma centres suggests that the threshold of HA is likely similar or slightly lower, given the perception of increased difficulty of THA.

Devereaux and colleagues have outlined the advantages of this trial design,[31] 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 over the other.
2. Differential performance, co-intervention, data collection, and outcome assessment are less likely than in conventional RCT.

With this approach, ethical concerns are reduced because all surgeries are conducted by surgeons with expertise and conviction concerning the procedures.[31]

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

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

Maximizing Patient Retention

Previous trials in hip fracture surgery have lost up to 50% of patients to follow-up.[15] To avoid this problem, the strategies outlined in **Figure 3** are used to minimize loss to follow-up. We have successfully used the majority of these strategies to maximize follow-up in other multi-centre studies. Key features of this strategy include: 1) excluding individuals who are likely to present problems with follow-up; 2) prior to hospital discharge, in addition to proving their own contact information, each patient provides the name and address of alternate contacts who are likely to be aware of the patient's whereabouts; 3) patients receive a reminder for their next follow up visit from the clinical research coordinator; and 4) follow-up visits coincide with standard fracture clinic visits. Additionally, patients can complete some study visits over the phone provided no radiographs are required.

Minimizing Co-Interventions and Contamination

Any patients who cross over from one treatment group to the other will be analyzed in the group to which they were allocated, maintaining the intention to treat approach of the analysis. Surgical co-interventions such as general, neurosurgical, or orthopaedic procedures performed in addition to the arthroplasty procedure, have the potential to confound outcomes. The standardization of key aspects of pre-operative and post-operative care, together with the expertise-based trial design will minimize the use of co-interventions in study patients. Clinical sites record the details of any major additional procedures performed, as well as the use of medications that affect bone, such as bisphosphonates, vitamin D, calcium, hormone replacement therapy, selective estrogen receptor modulators, calcitonin, and anabolic steroid therapy.

Maximizing Protocol Adherence

Given the inherent variability in practice patterns among orthopaedic surgeons, we believe it is important to ensure that surgeons adhere as closely as possible to the surgical management protocol. The feasibility of this large study involving multiple centres further depends upon minimal changes from current practice. Our study protocol closely follows currently accepted practice in the management of patients with femoral neck fractures. We therefore anticipate high compliance with our protocol.

Statistical Plan

Sample Size Determination

The choice of sample size is based upon a comparison of THA versus HA for the primary outcome (unplanned secondary procedures). 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 [14]. 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**) [14, 32-36].

Table 3a: Sample Size Calculations Comparing Total Hip Arthroplasty (THA) and Hemi-Arthroplasty (HA)

Studies included in a meta-analysis comparing THA with HA for the outcome of reoperation at one year

Study	THA Reoperation Rate	HA Reoperation Rate
van den Bekerom 2010 [32]	5/110 (4.5%)	1/136 (0.7%)
Baker 2006 [33]	4/36 (11.1%)	2/39 (5.1%)
Blomfeldt 2007 [34]	4/56 (7.1%)	3/57 (5.3%)
Keating 2006 [35]	6/63 (9.5%)	5/64 (7.8%)
Macaulay 2008 [36]	1/16 (6.25)	0/23 (0%)

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)

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.[37] 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 corresponding 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 [unpublished data]. 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.

Table 3b: Sample Size Calculations Comparing Total Hip Arthroplasty (THA) and Hemi-Arthroplasty (HA)

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

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

RRR = Relative Risk Reduction

For the secondary outcomes, an important difference in SF-12 is considered to correspond to a moderate effect as reported by Cohen as well as a minimally important difference in the SF-12 as reported by Ware.[38, 39] 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,[40] 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.[41] In this study, at least 90 patients (45 per group) would be required to detect this difference (alpha level=0.05, beta=0.20, σ =15). Previous studies have found a standard deviation of 0.20 for the EQ-5D.[42] 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.

Primary Analyses

All outcome analyses will be performed by an intention to treat approach. To evaluate the effect of THA versus HA on time to unplanned 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); and 5) Participating centre. Results

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

Secondary Analyses

As a secondary analysis, we will adjust for additional baseline factors when examining the effect of THA versus HA on time to unplanned secondary procedures (the primary outcome). This will be a Cox proportional hazards model which will include the same variables that are included in our primary analysis, and additionally adjusting for 1) Gender, 2) Surgical approach, and 3) Head size, by including these as independent variables. Results will be reported as hazard ratios with 95% confidence intervals.

A generalized linear model will estimate the effect of THA versus HA 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 (50 to 80 years or greater than 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); and 5) Participating centre.

Cox proportional hazards modeling will estimate the relative effect of THA versus HA 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.

Interim Analyses

The approach to interim analyses is guided by a desire to avoid spuriously inflated estimates of treatment effect.[43] 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. 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.

Data Management

The Case Report Forms (CRFs) are the primary data collection tool for the study. An Electronic Data Capture system (iDataFax) is being used to submit data to the Methods Centre located at McMaster University. Upon receipt of the data, the personnel at the Methods Centre make a visual check of the data and they query all missing data, implausible data, and inconsistencies.

Sensitivity Analyses

We will perform some sensitivity analyses to assess the robustness of the primary results. First, we will perform a competing risk analysis using Fine and Gray method to account for death as a competing risk.[44] Second, we will use the random-effects analysis with a centre as a random-effect to account for the possibility of the centre effect or clustering within a centre. Lastly, based on the pilot results we anticipate some cross-overs during the trial—we will monitor these and perform some sensitivity analysis to assess their impact. All analyses will be performed using SAS 9.2 (Cary, NC).

Missing Data

Patients who are lost or withdrawn from the study prior to full 24 month follow-up will be censored at their last visit where evaluation of the primary endpoint was completed.

Data Monitoring Committee

The purpose of the Data Monitoring Committee (DMC) is to advise the HEALTH Investigators regarding the continuing safety of study participants. The DMC consists of the Chair, who is an orthopaedic surgeon, one biostatistician, and two additional orthopaedic surgeons. All members are independent of the trial investigators, and have neither financial nor scientific conflicts of interest with the trial. Further details regarding the DMC can be found in the DMC Charter, available from the corresponding author.

ETHICAL CONSIDERATIONS

All patients (or their legally authorized representative) included in this study will sign a consent form that describes this study and provides sufficient information for patients to make an informed decision about their participation. All participating centres will submit the consent form with the protocol for review and approval by their local research ethics board (REB) or institutional review board (IRB) for the study. Centres will obtain written consent from every patient, using the REB/IRB-approved consent form, before that patient undergoes any study procedure. Any amendments to the study protocol which may affect the conduct of the study, or the potential safety of or benefits to patients will require a formal amendment to the protocol requiring approval by McMaster University's REB and local research ethics boards for clinical sites. Any protocol amendments will be communicated to investigators, REB/IRB, trial participants, and trial registries as necessary.

Information about study patients will be kept confidential and will be managed in accordance with the following rules: (1) All study-related information will be stored securely at the clinical site; (2) All study patient information will be stored in locked file cabinets and accessible only to study personnel; (3) All CRFs will be identified only by a coded patient number and initials; (4) All records that contain patient names, or other identifying information, will be stored separately from the study records that are identified only by the coded patient number and initials; and (5) All local databases will be password protected.

DISSEMINATION

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

Only the Methods Centre will have access to the full trial dataset. Data for the primary publication will be analyzed exclusively by the Methods Centre. Requests for access to the full trial dataset for secondary publications are encouraged and can be initiated through a written request to Methods Centre personnel.

DISCUSSION

Previous orthopaedic trials have addressed the effect of THA versus HA on patient outcomes; however, the trials conducted to date are limited by small sample sizes, lack of concealed randomization, differential expertise biases,[13] and most were single centre initiatives that lacked sufficient power to inform surgical practice. Orthopaedic surgeons appear to currently favor HA, although current evidence suggests superior patient-important outcomes with THA.[14, 31] The HEALTH trial will aim to resolve these controversies by establishing the effectiveness of each method of arthroplasty. This will have important clinical implications as each treatment is easily applicable and already in use in orthopaedic practice.

The HEALTH trial will address and overcome many of the limitations of previous orthopaedic hip fracture trials. Firstly, the study sample size of 1,434 patients is sufficient to detect small, but important differences in outcomes, and will ensure that our study objectives are met. Secondly, using an expertise-based RCT has many advantages over traditional orthopaedic hip studies, including eliminating differential performance and differential outcome assessment and reducing the number of crossovers and ethical concerns associated with randomization.[13] Furthermore, the HEALTH trial has stringent methodological safeguards against bias including: the use of a centralized system to randomize patients; blinding data analysts and the Steering Committee; standardization and documentation of pre-operative care, peri-operative care and post-operative care; the use of strategies to limit loss to follow up; and adjudication of trial events by an independent Central Adjudication Committee.

A key limitation of the HEALTH trial is that surgeons and patients cannot be blinded to the surgical arms. This leaves the assessment of outcomes and decisions to re-operate vulnerable to bias. We have limited this bias by using an objective primary outcome (unplanned secondary procedures) and by centrally adjudicating all primary outcome events using a group of independent orthopaedic surgeons. Additionally, we do not allow family members or friends to answer questionnaires on behalf of cognitively impaired patients, so some secondary outcomes will only apply to patients who are not cognitively impaired. Our trial is limited to shorter-term outcomes; up to two years following the initial surgery.

The results of the HEALTH trial will be an important contribution to orthopaedic surgical literature and likely lead to changes in orthopaedic practice. Identifying the optimal approach to arthroplasty has the potential to improve the lives of hundreds of thousands of patients and to reduce the economic burden associated with hip fractures. If this trial shows that one approach is superior to the other, it will revolutionize the treatment of hip fractures globally, and may potentially lead to the establishment of new clinical guidelines for treatment of displaced femoral neck fractures. In addition to the clinical impact, the HEALTH trial also has the potential to impact orthopaedic trial conduct. With this trial we will build collaborative relationships among countries and between clinical centres. This trial will also contribute to challenging the dogma that surgical trials are doomed to small single centre initiatives.

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COMPETING INTEREST STATEMENT

The authors have no competing interests to report.

REFERENCES

1. Cooper C, Campion G, Melton LJ, 3rd. Hip fractures in the elderly: a world-wide projection. *Osteoporos Int* 1992;2:285–9.
2. Dhanwal DK, Dennison EM, Harvey NC, et al. Epidemiology of hip fracture: worldwide geographic variation. *Indian J Orthop* 2011;45(1):15–22.
3. Johnell O, Kanis JA. An estimate of the worldwide prevalence, mortality and disability associated with hip fracture. *Osteoporos Int* 2004;15:897–902.
4. Iorio R, Schwartz B, Macaulay W, et al. Surgical treatment of displaced femoral neck fractures in the elderly: a survey of the American association of hip and knee surgeons. *Arthrop* 2006;21(8):1124-33.
5. Cummings SR, Rubin SM, Black D. The future of hip fractures in the United States. Numbers, costs, and potential effects of postmenopausal estrogen. *Clin Orthop Relat Res* 1990;252:163–6.
6. Papadimitropoulos EA, Coyte PC, Josse RG, et al. Current and projected rates of hip fracture in Canada. *CMAJ* 1997;157:1357-63.
7. AAOS urges hip fracture reform. American Academy of Orthopaedic Surgeons Bulletin 1999;47.
8. Moran CG, Wenn RT, Sikand M, et al. Early mortality after hip fracture: is delay before surgery important? *J Bone Joint Surg* 2005;87:483-89.
9. Jongjit J, Komsopapong L, Songjakkaew P, et al. Health-related quality of life after hip fracture in the elderly community-dwelling. *Southeast Asian J Trop Med Public Health* 2003;34:670-4.
10. Carrière G. Hip fracture outcomes in the household population. *Health Rep* 2007;18(4):37-42.
11. Cooper C, Campion G, Melton LJ. Hip fractures in the elderly: a world-wide projection. *Osteoporos Int* 1992;2:285–9.
12. Hopley C, Stengel D, Ekkernkamp A, et al. Primary total hip arthroplasty versus hemiarthroplasty for displaced intracapsular hip fractures in older patients: systematic review. *BMJ* 2010;340:c2332.
13. Liao L, Zhao Jm, Su W, et al. A meta-analysis of total hip arthroplasty and hemiarthroplasty outcomes for displaced femoral neck fractures. *Arch Orthop Trauma Surg* 2012;132(7):1021-9.
14. Burgers PTPW, Van Geene AR, Van den Bekerom MPJ, et al. Total hip arthroplasty versus hemiarthroplasty for displaced femoral neck fractures in the healthy elderly: a meta-analysis and systematic review of randomized trials. *Int Orthop* 2012;36:1549-60.
15. Bhandari M, Devereaux PJ, Tornetta P 3rd, et al. Operative management of displaced femoral neck fractures in elderly patients. An international survey. J Bone Joint Surg Am 2005;87:2122-30.
16. Pandis N. Randomization. Part 2: Minimization. *Am J Orthod Dentofacial Orthop* 2011;140(6):902-4.
17. Gillespie WJ. Extracts from "clinical evidence": hip fracture. *BMJ* 2001;322:968-75.
18. McHorney CA, Ware JE Jr, Rogers W, et al. The validity and relative precision of MOS short- and long-form health status scales and Dartmouth COOP charts. Results from the medical outcomes study. *Med Care* 1992;30(5 suppl):MS253-65.
19. Bellamy N, Buchanan WW, Goldsmith CH, et al. Validation of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol* 1988;15:1833-40.

20. Brooks R, Rabin RE, de Charro F, (Eds). The Measurement and Valuation of Health Status Using EQ-5D: A European Perspective. Dordrecht, The Netherlands: Kulwer Academic Publishers 2003.
21. Podsiadlo D, Richardson S. The timed 'up and go' test: a test of basic functional mobility for frail elderly persons. *J of Am Geri Soc* 1991;39(2):142-8.
22. Ware JE, Kosinski M, Keller SD. A 12-item short-form health survey: construction of scales and preliminary tests of reliability and validity. *Med Care* 1996;34:220-33.
23. Dattani R, Slobogean GP, O'Brien PJ, et al. Psychometric analysis of measuring functional outcomes in tibial plateau fractures using the Short Form 36 (SF-36), Short Musculoskeletal Function Assessment (SMFA) and the Western Ontario McMaster Osteoarthritis (WOMAC) questionnaires. *Injury* 2013;44(6):825-9.
24. Laflamme GY, Rouleau DM, Leduc S, et al. The Timed Up and Go test is an early predictor of functional outcome after hemiarthroplasty for femoral neck fracture. J Bone Joint Surg Am. 2012;94(13):1175-9.
25. McMeeken J, Stillman B, Story I, et al. The effects of knee extensor and flexor muscle training on the timed-up-and-go test in individuals with rheumatoid arthritis. *Physiother Res Int* 1999;4(1):55-67.
26. Shumway-Cook A, Brauer S, Woollacott M. Predicting the probability for falls in community-dwelling older adults using the Timed Up & Go Test. *Phys Ther* 2000;80(9):896-903.
27. Ravikumar KJ, Marsh G. Internal fixation versus hemiarthroplasty versus total hip arthroplasty for displaced subcapital fractures of femur -13 year results of a prospective randomised study. *Injury* 2000;31:793-7.
28. Callaghan JJ, Heekin RD, Savory CG, et al. Evaluation of the learning curve associated with uncemented primary porous-coated anatomic total hip arthroplasty. *Clin Orthop Relat Res* 1992;282:132-44.
29. Ellinor N, Lindelof N, Rosendahl E, et al. Prognostic validity of the Timed Up-and-Go test, staff's global judgement and fall history in evaluating fall risk in residential care facilities. *Age Ageing* 2008;37:442-8.
30. Katz JN, Losina E, Barrett J, et al. Association between hospital and surgeon procedure volume and outcomes of total hip replacement in the United States medicare population. *J Bone Joint Surg Am* 2001;83-A(11):1622-9.
31. Devereaux PJ, Bhandari M, Clarke M, et al. Need for expertise based randomised controlled trials. BMJ 2005;330:88-91.
32. van den Bekerom MP, Hilverdink EF, Sierevelt IN, et al. A comparison of hemiarthroplasty with total hip replacement for displaced intracapsular fracture of the femoral neck: a randomised controlled multicentre trial in patients aged 70 years and over. J Bone Joint Surg Br. 2010;92(10):1422-8.
33. Baker RP, Squires B, Gargan MF, et al. Total hip arthroplasty and hemiarthroplasty in mobile, independent patients with a displaced intracapsular fracture of the femoral neck. A randomized, controlled trial. J Bone Joint Surg Am. 2006;88(12):2583-9.
34. Blomfeldt R, Törnkvist H, Eriksson K, et al. A randomised controlled trial comparing bipolar hemiarthroplasty with total hip replacement for displaced intracapsular fractures of the femoral neck in elderly patients. J Bone Joint Surg Br. 2007;89(2):160-5.

35. Keating JF, Grant A, Masson M, et al. Displaced intracapsular hip fractures in fit, older people: a randomised comparison of reduction and fixation, bipolar hemiarthroplasty and total hip arthroplasty. *Health Technol Assess* 2005:9;1-65.
36. Macaulay W, Nellans KW, Garvin KL, et al. Prospective randomized clinical trial comparing hemiarthroplasty to total hip arthroplasty in the treatment of displaced femoral neck fractures. J Arthroplasty. 2008;23(6 Suppl 1):2-8.
37. Collett D. Modelling Survival Data in Medical Research. London, UK: Chapman & Hall 1994.
38. Cohen J. Statistical Power Analysis For The Behavioral Sciences. 2nd editions. Hillsdale, NJ: Lawrence Erlbaum Associates 1988.
39. Ware JE, Sherbourne CD. The MOS 36-item short form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30:473-83.
40. Jaglal S, Lakhani Z, Schatzker J. Reliability, validity, and responsiveness of the lower extremity measure for patients with a hip fracture. *J Bone Joint Surg Am* 2000;82:955-62.
41. Tubach F, Ravaud P, Baron G, et al. Evaluation of clinically relevant changes in patient reported outcomes in knee and hip osteoarthritis: The minimal clinically important improvement. *Ann Rheum Dis* 2005;64:29-33.
42. Tidermark J, Ponzer S, Svensson O, et al. Internal fixation compared with total hip replacement for displaced femoral neck fractures in the elderly: a randomised, controlled trial. *J Bone Joint Surg Br* 2003;85:380–8.
43. Montori VM, Devereaux PJ, Adhikari NK, et al. Stopping randomized clinical trials early for benefit: a protocol of the study of trial policy of interim truncation-2 (STOPIT-2). *Trials* 2009;10:49.
44. Fine J, Gray R. A proportional hazards model for the sub-distribution of a competing risk. *J Am Stat Assoc* 1999;94:496-509.

FIGURE LEGEND

Figure 1: Expertise-Based Randomized Controlled Trial
An expertise-based randomized controlled trial design randomizes participants to surgeons with expertise in surgery A or to surgeons with expertise in surgery B.

Figure 2: Schedule of Events
** Complete forms when and/or if applicable*

Figure 3: Strategies to Enhance Follow-Up Rates

Hip Fracture Evaluation with Alternatives of Total Hip Arthroplasty versus Hemi-Arthroplasty (HEALTH): Protocol for a Multi-Centre Randomized Trial

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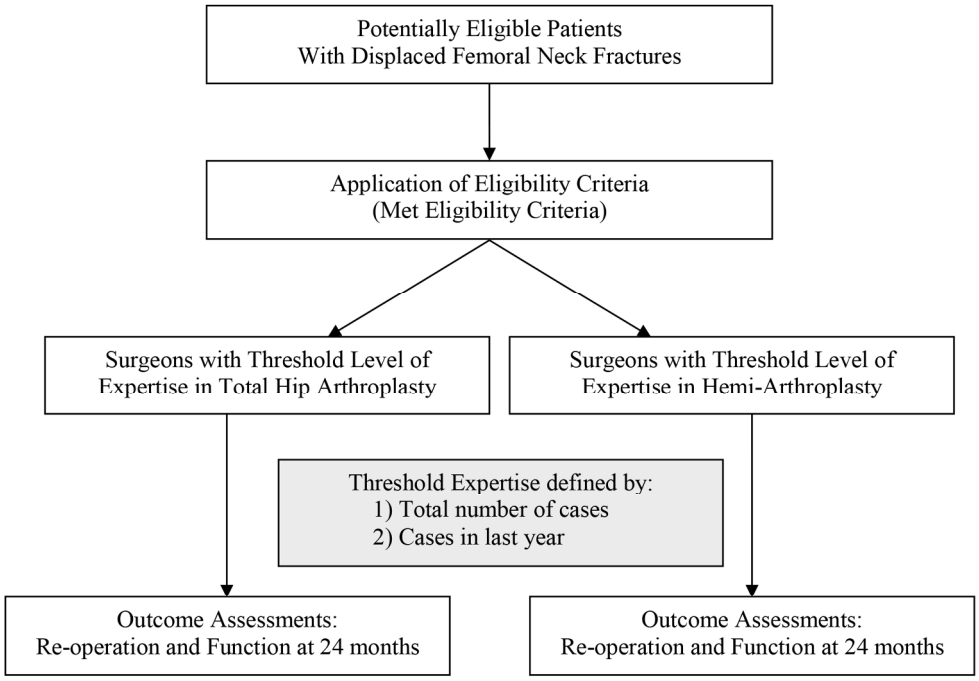

172x121mm (300 x 300 DPI)

Radiographs & Event Forms	Pre-Surgery			Surgery	Post Surgery								
	Screening	Enrollment	Baseline	(Day 0)	≤ 48 hrs Post Surgery	Discharge	1 wk	10 wk	6 mo	9 mo	12 mo	18 mo	24 mo
Patient Contact		•			•	•	•	•	•	•	•	•	•
Radiographs			•		•			•			•		•
Screening	•												
Informed Consent		•											
Randomization		•											
Baseline			•										
Surgical Report				•									
Post-Op Care					•								
Clinic or Telephone Follow-Up							•	•	•	•	•	•	•
Secondary Procedure					*		*	*	*	*	*	*	*
Adverse Event				*	*		*	*	*	*	*	*	*
Timed Up and Go								•	•		•		•
SF-12							•	•	•	•	•	•	•
WOMAC							•	•	•	•	•	•	•
EQ-5D							•	•	•	•	•	•	•
Missed Follow-Up						*	*	*	*	*	*	*	
Early W/D						*	*	*	*	*	*	*	*

171x114mm (300 x 300 DPI)

Before the study begins	At screening	At baseline	During the study	For patients who are difficult to contact
• Create a study identity that includes a logo on all study documents • Train research personnel in maintaining participant confidentiality • Ensure all study personnel are aware of study procedures	• Exclude participants who are likely to be difficult to follow for the duration of the trial (e.g. no fixed addresss, patients with dementia and no family support) • Be explicit about follow up procedures including when to expect contact from study staff, how often, and what type of contact (in person, email, phone etc.)	• Collect several personal contacts including friends or family members to assist with locating patients later • Ensure informed consent is conducted in an appropriate manner, including using examples and explanations that are accessible to a lay audience	• Provide participants with a choice of email, phone, and/or in-clinic visits when appropriate (i.e. when no radiographs are required) • Be flexible on scheduling in-clinic visits • Ensure participants can easily contact study personnel by providing them with contact informatio nthat is easy to access • Routinely verify that the participant's contact information is up to date	• Try previously disconnected phone numbers • Search online or in telephone books for updated contact information • Search the hospital's database for hospital admissions • Try to contact participants form a different phone number or at a different time of day • Hold regular staff meetings to brainstorm creative ways to locate participants who are dificult to contact

168x140mm (300 x 300 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	1-22
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	20
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	20-22
	5b	Name and contact information for the trial sponsor	N/A
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	20
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	14-15, 20-22

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	4-5
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4-5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5-6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	11
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9-10

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11-13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	11
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6-7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6-7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6-7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9-10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8-9
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	14
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12-14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14-15
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	14
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	7-9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	15

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
	31b	Authorship eligibility guidelines and any intended use of professional writers	20
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Hip Fracture Evaluation with ALternatives of Total Hip Arthroplasty versus Hemi-Arthroplasty (HEALTH): Protocol for a Multi-Centre Randomized Trial

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Hip Fracture Evaluation with Alternatives of Total Hip Arthroplasty versus Hemi-Arthroplasty (HEALTH): Protocol for a Multi-Centre Randomized Trial

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ABSTRACT

Introduction

Hip fractures are a leading cause of mortality and disability worldwide and the number of hip fractures is expected to rise to over 6 million per year by 2050. The optimal approach for the surgical management of displaced femoral neck fractures remains unknown. Current evidence suggests the use of arthroplasty; however, there is lack of evidence regarding whether patients with displaced femoral neck fractures experience better outcomes with total hip arthroplasty (THA) or hemi-arthroplasty (HA). The HEALTH trial compares outcomes following THA versus HA in patients 50 years of age or older with displaced femoral neck fractures.

Methods and Analysis

HEALTH is a multi-centre, randomized controlled trial where 1,434 patients 50 years of age or older with displaced femoral neck fractures from international sites, are randomized to receive either THA or HA. Exclusion criteria include associated major injuries of the lower extremity, hip infection(s) and a history of frank dementia. The primary outcome is unplanned secondary procedures and the secondary outcomes include functional outcomes, patient quality of life, mortality, and hip-related complications – both within two years of the initial surgery. We are using minimization to ensure balance between intervention groups for the following factors: age, pre-fracture living, pre-fracture functional status, American Society for Anesthesiologists (ASA) Class, and centre number. Data analysts and the HEALTH Steering Committee are blinded to surgical allocation throughout the trial. Outcome analysis will be performed using a Chi-square test (or Fisher's exact test) and Cox proportional hazards modeling estimate. All results will be presented with 95% confidence intervals.

Ethics and Dissemination

The HEALTH trial has received local and McMaster University Research Ethics Board (REB) approval (REB#: 06-151). Results from the primary manuscript will be disseminated through publications in academic journals and presentations at relevant orthopaedic conferences. We will communicate trial results to all participating sites. Participating sites will communicate results with patients who have indicated an interest in knowing the results.

Trial Registration

The HEALTH trial is registered with clinicaltrials.gov (NCT00556842).

STRENGTHS AND LIMITATIONS

Strengths

- This study has a large sample size of 1,434 patients in order to detect small but important differences in outcomes.
- We are utilizing an expertise-based randomized controlled trial design to help to eliminate differential performance and differential outcome assessments and reduce crossovers and ethical concerns associated with randomization.
- The study has stringent methodological safeguards against bias including: use of a centralized randomization system; blinding data analysts and the Steering Committee; standardization and documentation; use of strategies to limit loss to follow up; and adjudication of trial events by an independent Central Adjudication Committee.

Limitation

- Surgeons and patients cannot be blinded to the surgical arms, leaving the assessment of outcomes and decisions to re-operate vulnerable to bias.
- We do not allow family members and friends to answer questionnaires on behalf of cognitively impaired patients, so some secondary outcomes will only apply to patients who are not cognitively impaired.
- The two year follow up limits the study to shorter-term outcomes.

INTRODUCTION

The number of hip fractures globally is expected to rise to over 6 million by the year 2050.[1, 2] Due to projected aging of the population, 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.[3-5] By the year 2040, the estimated annual health care costs associated with hip fractures will reach $9.8 billion in the United States and $650 million in Canada.[6] 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.[7] In the elderly, hip fractures are associated with a 30% mortality rate at 1 year post-injury and profound temporary,[8] and often permanent, impairment of independence and quality of life.[9, 10] Worldwide, 4.5 million people are disabled from hip fractures yearly with the number of persons living with disability expected to increase to 21 million in the next 40 years.[3, 5, 11] The disability adjusted life-years lost as a result of hip fractures ranks in the top 10 of all causes of global disability.[3]

Inconclusive Clinical Evidence

Femoral neck fractures may be either non-displaced (i.e., very little separation at the fracture site, about one third of femoral neck fractures) or displaced (i.e., greater separation at the fracture site, about two thirds of femoral neck fractures). Orthopaedic surgeons often treat non-displaced fractures with internal fixation and displaced fractures with arthroplasty, which is also known as joint replacement.

We conducted a comprehensive literature search to identify all studies investigating total hip arthroplasty (THA; involves replacing the femoral head and the acetabulum) compared to hemi-arthroplasty (HA; involves replacing the femoral head only) for displaced femoral neck fractures. We identified a recent meta-analysis of 14 studies (N=1,890 patients).[12] This meta-analysis demonstrated a lower risk of re-operation after THA compared with HA (relative risk 0.57, 95% CI 0.34 to 0.96); however, this effect was mainly driven by randomized controlled trials (RCTs) without concealed treatment allocation. THA consistently resulted in better hip function (Harris Hip Score, weighted mean difference 5.4, 95% CI 2.7 to 8.2) after follow-up intervals of 12 to 48 months.[12] We also identified two additional meta-analyses that provide comparisons of THA and HA.[13, 14] Liao et al pooled RCTs of THA (N=403 patients) versus HA (N=425 patients),[13] and found reductions in the risk of secondary procedures and wound infection with THA. Furthermore, Liao et al reported that the mobility rate in THA was better than in HA. Burgers et al performed a meta-analysis of eight RCTs (N=986 patients) that suggested similar rates of secondary procedures,[14] one year mortality, major complications, and minor complications with THA and HA, but large benefits in patient function with THA. Despite the benefits that THA confers regarding functional outcomes, secondary procedures, and infection rates, both meta-analyses reported higher hip dislocation rates with THA.

In a survey of 298 surgeons who were members of the Orthopaedic Trauma Association or affiliated with AO International, 94-96% of surgeons agreed that arthroplasty is the preferred treatment option in patients over 80 years of age with displaced femoral neck fractures.[15] In addition, 73% of surgeons surveyed preferred HA to THA.[15] In summary, current evidence suggests substantial benefits of THA over HA in decreased pain and improved function, but also increased rates of dislocation associated with THA, with similar rates of secondary procedures and mortality with the two procedures. Despite the apparent benefits of THA over HA, surgeons

more often prefer HA to treat displaced femoral neck fractures. Previous trials comparing these two approaches were limited by methodological issues, so the current trial aims to determine the effectiveness of THA compared to HA using a large sample size and high-quality methodology.

Study Objectives

Our primary objective is to assess the impact of THA versus HA on rates of unplanned secondary procedures at two years in individuals with displaced femoral neck fractures.

Secondary objectives are:

1. To examine the effect of THA versus HA 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 THA versus HA on mortality.
3. To evaluate the effect of THA versus HA 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 (e.g. pseudotumor), heterotopic ossification, abductor failure, implant wear and corrosion, osteolysis, neurovascular injury, decreased function, and pain.

METHODS AND ANALYSIS

Overview of Study Design

HEALTH is a multi-centre, concealed RCT of 1,434 elderly patients who have sustained a displaced femoral neck fracture. We are using minimization, a form of randomization, to determine patient allocation. Surgeons across North America, Europe, Australia, and Asia are participating. In conventional surgical hip fracture trials, all surgeons involved in the trial have performed both THA and HA based on the randomization process. HEALTH utilizes an expertise-based randomized trial design that allocates patients to surgeons with expertise in THA or HA (**Figure 1**). Based upon their expertise, surgeons perform either THA or HA. Surgeons who feel confident enough to perform both surgical strategies perform both THA and HA.

Patient Selection

Eligibility Criteria

The inclusion criteria are: 1) Adult men or women aged 50 years and older (with no upper age limit); 2) Fracture of the femoral neck confirmed with antero-posterior (AP) and lateral radiographs or computed tomography (CT) 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 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); and 10) Assurance that surgeons with expertise in both THA and HA are available to perform surgery.

The exclusion criteria are: 1) Patient not suitable for HA (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 (e.g. 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 (e.g. 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 two years); 7) Likely problems, in the judgment of the investigators, with maintaining follow-up (e.g. patients with no fixed address, report a plan to move out of town, alcohol abuse issues, or intellectually challenged patients without adequate family support); and 8) Patients whose fracture occurred as a result of an act of violence.

Patient Recruitment and Screening

The first patient was randomized into the vanguard phase of this trial on 21 January 2009. After a brief pause in enrollment between the vanguard and definitive phase, the first definitive patient was randomized on 8 October 2013. Enrollment is ongoing at the time pf publication and is expected to be completed by December 2016. All patients presenting to participating surgeons with a diagnosed femoral neck fracture amenable to arthroplasty are screened for participation in the HEALTH trial. Such patients are classified as: 1) Excluded (if they do not meet the eligibility criteria); 2) Missed (presumed eligible but missed due to error or staff availability); or 3) Included (eligible and randomized). Study personnel obtain informed consent from all eligible patients. If a patient lacks capacity and is deemed unable to consent, study personnel may obtain informed consent from the patient's legally authorized representative and assent from the patient.

Randomization

We are ensuring concealment of allocation by using a centralized 24-hour computerized randomization system that will allow internet-based randomization. Patients are the unit of randomization. To protect against prognostic imbalance between groups, we are using minimization to ensure balance between intervention groups for several patient factors. The minimization approach takes into account each pre-identified prognostic variable and sums over the variables to allocate each patient to the treatment that will minimize the differences between groups for those prognostic variables. Unlike stratified randomization, minimization works toward minimizing the total imbalance for all factors together instead of considering mutually exclusive subgroups (strata).[16] Based on our international survey of surgeons,[15] and current evidence,[17] we are minimizing for the following prognostic factors: 1) Age (i.e., 50 to 80 years or greater than 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); and 5) Participating centre.

Study Interventions

Total Hip Arthroplasty

In the THA group, we are not including minimally invasive THA (i.e., 2 incision approaches) or hinged prostheses or capture cups. To optimize feasibility and applicability of results, we did not standardize the surgical approach including the use of cemented components, the implant manufacturer, or femoral head size. We are documenting the manufacturer, implant material, and bearing surface of the implant.

Hemi-Arthroplasty

Surgeons are to use modern implants for HA excluding non-modular, non-canal filling unipolar implants such as Moore's and Thompson's prostheses. We did not standardize the choice of modular unipolar versus bipolar HA nor whether implants are inserted with cement or with a press-fit design. We are documenting the manufacturer, implant material, and bearing surface of the implant.

Standardization of Procedures and Peri-Operative Care

To ensure similar peri-operative regimens, we recommend that participating centres standardize key aspects of pre- and post-operative care. For pre-operative care, we recommend standardization of the following: (1) Pre-operative antibiotic prophylaxis (e.g. cephalosporins or equivalent coverage); (2) Thromboprophylaxis (e.g. oral anticoagulation drugs, thromboembolic deterrent 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)); and (3) Medical consultation to optimize condition prior to surgery. For post-operative care, we recommend standardization of the following: (1) Antibiotic prophylaxis (e.g. 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 are weightbearing as tolerated, and then advanced according to the attending surgeon's best judgment; (4) 600 mg calcium by mouth daily and 1000 IU vitamin D per day (provided there are no contraindications) and further investigation and treatment of osteoporosis as recommended by a local osteoporosis expert/consultant; and (5) Appropriate nutritional assessment with administration of oral micronutrient feeds as needed. Due to a lack of evidence favouring a particular approach, we are recording but did not standardize the following: (1) Use of pre-operative traction; (2) Surgical delay; (3) Type of anesthetic (i.e., general or regional); and (4) Patient participation in physiotherapy and rehabilitation.

Study Outcomes

Primary Study Outcome

The primary outcome is any unplanned secondary procedure within 2 years of the initial hip 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**).

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

Specific unplanned secondary procedures	Classification of the reason for secondary

include:	procedures is as follows:
• Closed reduction of hip dislocation • Open reduction of hip dislocation • Open reduction of fracture • Soft tissue procedure • Insertion of antibiotic spacer • Full implant exchange • Partial implant exchange – stem only • Partial implant exchange - head only • Partial implant exchange - liner only • Partial implant exchange - head and liner • Partial implant exchange – acetabular component only • Partial implant exchange – acetabular component and head • Implant adjustment – re-orientation of the stem • Implant adjustment – re-orientation of the acetabulum component • Implant removal with no replacement • Excision heterotopic ossification • Supplementary fixation	• Treat a peri-prosthetic fracture • Treat hip instability or dislocation • Treat infection – superficial • Treat infection – deep • Treat wound necrosis • Treat another wound healing problem • Remove heterotopic ossification • Manage abductor failure • Manage another soft tissue problem (i.e. pseudotumor) • Correct implant failure –loosening or subsidence • Correct implant failure - breakage • Treat implant wear • Treat osteolysis • Treat implant corrosion • Improve function • Relieve pain

Secondary Study Outcomes

Secondary outcomes include: 1) Functional outcome and quality of life measured using self-administered and interview-administered questionnaires. 2) The effect of THA versus HA on mortality; 3) 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 (e.g. pseudotumor), heterotopic ossification, abductor failure, implant wear and corrosion, osteolysis, neurovascular injury, decreased function, or pain.

Functional outcome and quality of life are measured using self-administered and interview-administered questionnaires. Functional outcome questionnaires include a generic health status measurement instrument (SF-12),[18] a hip function and pain questionnaire (WOMAC),[19] a health outcome measure (EQ-5D),[20] and a functional mobility test (TUG).[21]

The SF-12 questionnaire 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). The instrument has been extensively validated and has demonstrated good construct validity, high internal

consistency, and high test-retest reliability.[22] It is frequently used in orthopaedics for evaluating fracture outcomes.

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.[19] It is a valid, reliable and responsive measure of outcome, and has been used in several studies involving a wide range of lower extremity conditions.[23]

The EQ-5D is a comprehensive, compact health status classification and health state preference system.[20] This questionnaire is widely used and has demonstrated validity and sensitivity in many populations.[20, 22] The EQ-5D is generalizable, as it is widely used in Europe, and will be useful for our definitive trial in which we will be including international sites.

The timed up and go test (TUG) involves observing the patient and documenting the time,[21] in seconds, it takes for the patient to rise from a standard arm chair, walk to a line on the floor 3 metres away, turn, return, ands sit down again. The TUG has been used in many clinical contexts including orthopaedics,[24] rheumatology,[25] and predicting geriatric falls.[26]

Adjudication of Study Events

The HEALTH Central Adjudication Committee (CAC) is comprised of five orthopaedic surgeons who specialize in hip surgery and have expertise in research methodology and experience with clinical trials. The CAC are reviewing: 1) Cases where fracture eligibility is in doubt; 2) Post-operative x-rays to assess the technical placement of prostheses; 3) All reported secondary procedures and fracture-related complications to determine if a secondary procedure and/or fracture-related complication meeting study criteria has occurred; and 4) Cases of mortality to confirm the cause of death. All centres submit digital x-rays to the HEALTH Methods Centre. We post all relevant patient records devoid of personal identifiers (i.e., case report forms and x-rays) on a specially designed, password-protected website for study adjudication. Adjudication occurs after patients have completed their two year follow-up. Any disagreements among the CAC members are resolved during conference calls. All decisions made by the Committee are final.

Study Follow Up

All patients are followed for a period of two years. At each follow up interval, patients' health status and outcomes are recorded. In addition, at the 2-year follow-up visit, the surgeon documents any secondary procedure that may be planned for the patient. **Figure 2** shows the schedule of events and assessments at each time point.

Our choice of a 2-year follow-up period is dictated by two factors. First, previous studies have reported that 75% of revision surgeries occur before 12 months for patients treated with arthroplasty for displaced femoral neck fractures.[27] Thus, we can expect that the majority of revision surgeries will occur within 2 years. Since increasing follow-up to beyond 2 years will yield little additional information on secondary procedure rates, efficient use of resources dictates a 2-year follow-up. Second, a full 2 years of follow-up will provide sufficient time to assess any potential gains in function and quality of life afforded by either surgical alternative.

Protecting Against Sources of Bias

Blinding

While surgeons, patients, and outcome assessors cannot be blinded to the surgical arms (i.e., THA or HA), data analysts and the Steering Committee will remain blinded throughout the trial. Secondary procedures, the primary outcome, are objective and lack of blinding introduces minimal threats to validity. Additionally, the HEALTH trial design eliminates differential expertise bias by establishing a minimal threshold for experience, as well as ensuring that all surgeons performing either THA or HA are dedicated to and have sufficient expertise with the procedure.

Surgeon Expertise

Surgeons participating in the HEALTH trial are asked to meet both of the following two criteria for expertise for either THA or HA: 1) Perform at least 50 procedures (either THA or HA) in their career (including residency experience in which they assumed responsibility for the procedure), and 2) Perform at least 5 procedures per year. Surgeons who meet the threshold for both THA and HA will perform both procedures, if no overwhelming bias in favour of one procedure is evident. A surgeon is 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 the threshold expertise criteria and must be present in the operating room for the critical aspects of the procedure (**Table 2**). Our decision to set 50 procedures as the threshold for experience is based upon previous studies examining learning curves and respective outcomes in patients undergoing THA.[28-30] Our survey of surgeons who are members of the Orthopaedic Trauma Association (OTA) or European AO International trauma centres suggests that the threshold of HA is likely similar or slightly lower, given the perception of increased difficulty of THA.

Devereaux and colleagues have outlined the advantages of this trial design,[31] 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 over the other.
2. Differential performance, co-intervention, data collection, and outcome assessment are less likely than in conventional RCT.

With this approach, ethical concerns are reduced because all surgeries are conducted by surgeons with expertise and conviction concerning the procedures.[31]

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

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

Maximizing Patient Retention

Previous trials in hip fracture surgery have lost up to 50% of patients to follow-up.[15] To avoid this problem, the strategies outlined in **Figure 3** are used to minimize loss to follow-up. We have successfully used the majority of these strategies to maximize follow-up in other multi-centre studies. Key features of this strategy include: 1) excluding individuals who are likely to present problems with follow-up; 2) prior to hospital discharge, in addition to proving their own contact information, each patient provides the name and address of alternate contacts who are likely to be aware of the patient's whereabouts; 3) patients receive a reminder for their next follow up visit from the clinical research coordinator; and 4) follow-up visits coincide with standard fracture clinic visits. Additionally, patients can complete some study visits over the phone provided no radiographs are required.

Minimizing Co-Interventions and Contamination

Any patients who cross over from one treatment group to the other will be analyzed in the group to which they were allocated, maintaining the intention to treat approach of the analysis. Surgical co-interventions such as general, neurosurgical, or orthopaedic procedures performed in addition to the arthroplasty procedure, have the potential to confound outcomes. The standardization of key aspects of pre-operative and post-operative care, together with the expertise-based trial design will minimize the use of co-interventions in study patients. Clinical sites record the details of any major additional procedures performed, as well as the use of medications that affect bone, such as bisphosphonates, vitamin D, calcium, hormone replacement therapy, selective estrogen receptor modulators, calcitonin, and anabolic steroid therapy.

Maximizing Protocol Adherence

Given the inherent variability in practice patterns among orthopaedic surgeons, we believe it is important to ensure that surgeons adhere as closely as possible to the surgical management protocol. The feasibility of this large study involving multiple centres further depends upon minimal changes from current practice. Our study protocol closely follows currently accepted practice in the management of patients with femoral neck fractures. We therefore anticipate high compliance with our protocol.

Statistical Plan

Sample Size Determination

The choice of sample size is based upon a comparison of THA versus HA for the primary outcome (unplanned secondary procedures). 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 [14]. 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**) [14, 32-36].

Table 3a: Sample Size Calculations Comparing Total Hip Arthroplasty (THA) and Hemi-Arthroplasty (HA)

Studies included in a meta-analysis comparing THA with HA for the outcome of reoperation at one year

Study	THA Reoperation Rate	HA Reoperation Rate
van den Bekerom 2010 [32]	5/110 (4.5%)	1/136 (0.7%)
Baker 2006 [33]	4/36 (11.1%)	2/39 (5.1%)
Blomfeldt 2007 [34]	4/56 (7.1%)	3/57 (5.3%)
Keating 2006 [35]	6/63 (9.5%)	5/64 (7.8%)
Macaulay 2008 [36]	1/16 (6.25)	0/23 (0%)

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)

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.[37] 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 corresponding 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 [unpublished data]. 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.

Table 3b: Sample Size Calculations Comparing Total Hip Arthroplasty (THA) and Hemi-Arthroplasty (HA)

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

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

RRR = Relative Risk Reduction

For the secondary outcomes, an important difference in SF-12 is considered to correspond to a moderate effect as reported by Cohen as well as a minimally important difference in the SF-12 as reported by Ware.[38, 39] 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,[40] 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.[41] In this study, at least 90 patients (45 per group) would be required to detect this difference (alpha level=0.05, beta=0.20, σ =15). Previous studies have found a standard deviation of 0.20 for the EQ-5D.[42] 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.

Primary Analyses

All outcome analyses will be performed by an intention to treat approach. To evaluate the effect of THA versus HA on time to unplanned 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); and 5) Participating centre. Results

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

Secondary Analyses

As a secondary analysis, we will adjust for additional baseline factors when examining the effect of THA versus HA on time to unplanned secondary procedures (the primary outcome). This will be a Cox proportional hazards model which will include the same variables that are included in our primary analysis, and additionally adjusting for 1) Gender, 2) Surgical approach, and 3) Head size, by including these as independent variables. Results will be reported as hazard ratios with 95% confidence intervals.

A generalized linear model will estimate the effect of THA versus HA 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 (50 to 80 years or greater than 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); and 5) Participating centre.

Cox proportional hazards modeling will estimate the relative effect of THA versus HA 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.

Interim Analyses

The approach to interim analyses is guided by a desire to avoid spuriously inflated estimates of treatment effect.[43] 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. 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.

Data Management

The Case Report Forms (CRFs) are the primary data collection tool for the study. An Electronic Data Capture system (iDataFax) is being used to submit data to the Methods Centre located at McMaster University. Upon receipt of the data, the personnel at the Methods Centre make a visual check of the data and they query all missing data, implausible data, and inconsistencies.

Sensitivity Analyses

We will perform some sensitivity analyses to assess the robustness of the primary results. First, we will perform a competing risk analysis using Fine and Gray method to account for death as a competing risk.[44] Second, we will use the random-effects analysis with a centre as a random-effect to account for the possibility of the centre effect or clustering within a centre. Lastly, based on the pilot results we anticipate some cross-overs during the trial—we will monitor these and perform some sensitivity analysis to assess their impact. All analyses will be performed using SAS 9.2 (Cary, NC).

Missing Data

Patients who are lost or withdrawn from the study prior to full 24 month follow-up will be censored at their last visit where evaluation of the primary endpoint was completed.

Data Monitoring Committee

The purpose of the Data Monitoring Committee (DMC) is to advise the HEALTH Investigators regarding the continuing safety of study participants. The DMC consists of the Chair, who is an orthopaedic surgeon, one biostatistician, and two additional orthopaedic surgeons. All members are independent of the trial investigators, and have neither financial nor scientific conflicts of interest with the trial. Further details regarding the DMC can be found in the DMC Charter, available from the corresponding author.

ETHICAL CONSIDERATIONS

All patients (or their legally authorized representative) included in this study will sign a consent form that describes this study and provides sufficient information for patients to make an informed decision about their participation. All participating centres will submit the consent form with the protocol for review and approval by their local research ethics board (REB) or institutional review board (IRB) for the study. Centres will obtain written consent from every patient, using the REB/IRB-approved consent form, before that patient undergoes any study procedure. Any amendments to the study protocol which may affect the conduct of the study, or the potential safety of or benefits to patients will require a formal amendment to the protocol requiring approval by McMaster University's REB and local research ethics boards for clinical sites. Any protocol amendments will be communicated to investigators, REB/IRB, trial participants, and trial registries as necessary.

Information about study patients will be kept confidential and will be managed in accordance with the following rules: (1) All study-related information will be stored securely at the clinical site; (2) All study patient information will be stored in locked file cabinets and accessible only to study personnel; (3) All CRFs will be identified only by a coded patient number and initials; (4) All records that contain patient names, or other identifying information, will be stored separately from the study records that are identified only by the coded patient number and initials; and (5) All local databases will be password protected.

DISSEMINATION

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

Only the Methods Centre will have access to the full trial dataset. Data for the primary publication will be analyzed exclusively by the Methods Centre. Requests for access to the full trial dataset for secondary publications are encouraged and can be initiated through a written request to Methods Centre personnel.

DISCUSSION

Previous orthopaedic trials have addressed the effect of THA versus HA on patient outcomes; however, the trials conducted to date are limited by small sample sizes, lack of concealed randomization, differential expertise biases,[13] and most were single centre initiatives that lacked sufficient power to inform surgical practice. Orthopaedic surgeons appear to currently favor HA, although current evidence suggests superior patient-important outcomes with THA.[14, 31] The HEALTH trial will aim to resolve these controversies by establishing the effectiveness of each method of arthroplasty. This will have important clinical implications as each treatment is easily applicable and already in use in orthopaedic practice.

The HEALTH trial will address and overcome many of the limitations of previous orthopaedic hip fracture trials. Firstly, the study sample size of 1,434 patients is sufficient to detect small, but important differences in outcomes, and will ensure that our study objectives are met. Secondly, using an expertise-based RCT has many advantages over traditional orthopaedic hip studies, including eliminating differential performance and differential outcome assessment and reducing the number of crossovers and ethical concerns associated with randomization.[13] Furthermore, the HEALTH trial has stringent methodological safeguards against bias including: the use of a centralized system to randomize patients; blinding data analysts and the Steering Committee; standardization and documentation of pre-operative care, peri-operative care and post-operative care; the use of strategies to limit loss to follow up; and adjudication of trial events by an independent Central Adjudication Committee.

A key limitation of the HEALTH trial is that surgeons and patients cannot be blinded to the surgical arms. This leaves the assessment of outcomes and decisions to re-operate vulnerable to bias. We have limited this bias by using an objective primary outcome (unplanned secondary procedures) and by centrally adjudicating all primary outcome events using a group of independent orthopaedic surgeons. Additionally, we do not allow family members or friends to answer questionnaires on behalf of cognitively impaired patients, so some secondary outcomes will only apply to patients who are not cognitively impaired. Our trial is limited to shorter-term outcomes; up to two years following the initial surgery. Therefore our results may not apply when considering longer term outcomes.

The results of the HEALTH trial will be an important contribution to orthopaedic surgical literature and likely lead to changes in orthopaedic practice. Identifying the optimal approach to arthroplasty has the potential to improve the lives of hundreds of thousands of patients and to reduce the economic burden associated with hip fractures. If this trial shows that one approach is superior to the other, it will revolutionize the treatment of hip fractures globally, and may potentially lead to the establishment of new clinical guidelines for treatment of displaced femoral neck fractures. In addition to the clinical impact, the HEALTH trial also has the potential to impact orthopaedic trial conduct. With this trial we will build collaborative relationships among

countries and between clinical centres. This trial will also contribute to challenging the dogma that surgical trials are doomed to small single centre initiatives.

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REFERENCES

1. Cooper C, Campion G, Melton LJ, 3rd. Hip fractures in the elderly: a world-wide projection. *Osteoporos Int* 1992;2:285–9.
2. Dhanwal DK, Dennison EM, Harvey NC, et al. Epidemiology of hip fracture: worldwide geographic variation. *Indian J Orthop* 2011;45(1):15–22.
3. Johnell O, Kanis JA. An estimate of the worldwide prevalence, mortality and disability associated with hip fracture. *Osteoporos Int* 2004;15:897–902.
4. Iorio R, Schwartz B, Macaulay W, et al. Surgical treatment of displaced femoral neck fractures in the elderly: a survey of the American association of hip and knee surgeons. *Arthrop* 2006;21(8):1124-33.
5. Cummings SR, Rubin SM, Black D. The future of hip fractures in the United States. Numbers, costs, and potential effects of postmenopausal estrogen. *Clin Orthop Relat Res* 1990;252:163–6.
6. Papadimitropoulos EA, Coyte PC, Josse RG, et al. Current and projected rates of hip fracture in Canada. *CMAJ* 1997;157:1357-63.
7. AAOS urges hip fracture reform. American Academy of Orthopaedic Surgeons Bulletin 1999;47.
8. Moran CG, Wenn RT, Sikand M, et al. Early mortality after hip fracture: is delay before surgery important? *J Bone Joint Surg* 2005;87:483-89.
9. Jongjit J, Komsopapong L, Songjakkaew P, et al. Health-related quality of life after hip fracture in the elderly community-dwelling. *Southeast Asian J Trop Med Public Health* 2003;34:670-4.
10. Carrière G. Hip fracture outcomes in the household population. *Health Rep* 2007;18(4):37-42.
11. Cooper C, Campion G, Melton LJ. Hip fractures in the elderly: a world-wide projection. *Osteoporos Int* 1992;2:285–9.
12. Hopley C, Stengel D, Ekkernkamp A, et al. Primary total hip arthroplasty versus hemiarthroplasty for displaced intracapsular hip fractures in older patients: systematic review. *BMJ* 2010;340:c2332.
13. Liao L, Zhao Jm, Su W, et al. A meta-analysis of total hip arthroplasty and hemiarthroplasty outcomes for displaced femoral neck fractures. *Arch Orthop Trauma Surg* 2012;132(7):1021-9.
14. Burgers PTPW, Van Geene AR, Van den Bekerom MPJ, et al. Total hip arthroplasty versus hemiarthroplasty for displaced femoral neck fractures in the healthy elderly: a meta-analysis and systematic review of randomized trials. *Int Orthop* 2012;36:1549-60.
15. Bhandari M, Devereaux PJ, Tornetta P 3rd, et al. Operative management of displaced femoral neck fractures in elderly patients. An international survey. J Bone Joint Surg Am 2005;87:2122-30.
16. Pandis N. Randomization. Part 2: Minimization. *Am J Orthod Dentofacial Orthop* 2011;140(6):902-4.
17. Gillespie WJ. Extracts from "clinical evidence": hip fracture. *BMJ* 2001;322:968-75.
18. McHorney CA, Ware JE Jr, Rogers W, et al. The validity and relative precision of MOS short- and long-form health status scales and Dartmouth COOP charts. Results from the medical outcomes study. *Med Care* 1992;30(5 suppl):MS253-65.
19. Bellamy N, Buchanan WW, Goldsmith CH, et al. Validation of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol* 1988;15:1833-40.

20. Brooks R, Rabin RE, de Charro F, (Eds). The Measurement and Valuation of Health Status Using EQ-5D: A European Perspective. Dordrecht, The Netherlands: Kulwer Academic Publishers 2003.
21. Podsiadlo D, Richardson S. The timed 'up and go' test: a test of basic functional mobility for frail elderly persons. *J of Am Geri Soc* 1991;39(2):142-8.
22. Ware JE, Kosinski M, Keller SD. A 12-item short-form health survey: construction of scales and preliminary tests of reliability and validity. *Med Care* 1996;34:220-33.
23. Dattani R, Slobogean GP, O'Brien PJ, et al. Psychometric analysis of measuring functional outcomes in tibial plateau fractures using the Short Form 36 (SF-36), Short Musculoskeletal Function Assessment (SMFA) and the Western Ontario McMaster Osteoarthritis (WOMAC) questionnaires. *Injury* 2013;44(6):825-9.
24. Laflamme GY, Rouleau DM, Leduc S, et al. The Timed Up and Go test is an early predictor of functional outcome after hemiarthroplasty for femoral neck fracture. J Bone Joint Surg Am. 2012;94(13):1175-9.
25. McMeeken J, Stillman B, Story I, et al. The effects of knee extensor and flexor muscle training on the timed-up-and-go test in individuals with rheumatoid arthritis. *Physiother Res Int* 1999;4(1):55-67.
26. Shumway-Cook A, Brauer S, Woollacott M. Predicting the probability for falls in community-dwelling older adults using the Timed Up & Go Test. *Phys Ther* 2000;80(9):896-903.
27. Ravikumar KJ, Marsh G. Internal fixation versus hemiarthroplasty versus total hip arthroplasty for displaced subcapital fractures of femur -13 year results of a prospective randomised study. *Injury* 2000;31:793-7.
28. Callaghan JJ, Heekin RD, Savory CG, et al. Evaluation of the learning curve associated with uncemented primary porous-coated anatomic total hip arthroplasty. *Clin Orthop Relat Res* 1992;282:132-44.
29. Ellinor N, Lindelof N, Rosendahl E, et al. Prognostic validity of the Timed Up-and-Go test, staff's global judgement and fall history in evaluating fall risk in residential care facilities. *Age Ageing* 2008;37:442-8.
30. Katz JN, Losina E, Barrett J, et al. Association between hospital and surgeon procedure volume and outcomes of total hip replacement in the United States medicare population. *J Bone Joint Surg Am* 2001;83-A(11):1622-9.
31. Devereaux PJ, Bhandari M, Clarke M, et al. Need for expertise based randomised controlled trials. BMJ 2005;330:88-91.
32. van den Bekerom MP, Hilverdink EF, Sierevelt IN, et al. A comparison of hemiarthroplasty with total hip replacement for displaced intracapsular fracture of the femoral neck: a randomised controlled multicentre trial in patients aged 70 years and over. J Bone Joint Surg Br. 2010;92(10):1422-8.
33. Baker RP, Squires B, Gargan MF, et al. Total hip arthroplasty and hemiarthroplasty in mobile, independent patients with a displaced intracapsular fracture of the femoral neck. A randomized, controlled trial. J Bone Joint Surg Am. 2006;88(12):2583-9.
34. Blomfeldt R, Törnkvist H, Eriksson K, et al. A randomised controlled trial comparing bipolar hemiarthroplasty with total hip replacement for displaced intracapsular fractures of the femoral neck in elderly patients. J Bone Joint Surg Br. 2007;89(2):160-5.

35. Keating JF, Grant A, Masson M, et al. Displaced intracapsular hip fractures in fit, older people: a randomised comparison of reduction and fixation, bipolar hemiarthroplasty and total hip arthroplasty. *Health Technol Assess* 2005:9;1-65.
36. Macaulay W, Nellans KW, Garvin KL, et al. Prospective randomized clinical trial comparing hemiarthroplasty to total hip arthroplasty in the treatment of displaced femoral neck fractures. J Arthroplasty. 2008;23(6 Suppl 1):2-8.
37. Collett D. Modelling Survival Data in Medical Research. London, UK: Chapman & Hall 1994.
38. Cohen J. Statistical Power Analysis For The Behavioral Sciences. 2nd editions. Hillsdale, NJ: Lawrence Erlbaum Associates 1988.
39. Ware JE, Sherbourne CD. The MOS 36-item short form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30:473-83.
40. Jaglal S, Lakhani Z, Schatzker J. Reliability, validity, and responsiveness of the lower extremity measure for patients with a hip fracture. *J Bone Joint Surg Am* 2000;82:955-62.
41. Tubach F, Ravaud P, Baron G, et al. Evaluation of clinically relevant changes in patient reported outcomes in knee and hip osteoarthritis: The minimal clinically important improvement. *Ann Rheum Dis* 2005;64:29-33.
42. Tidermark J, Ponzer S, Svensson O, et al. Internal fixation compared with total hip replacement for displaced femoral neck fractures in the elderly: a randomised, controlled trial. *J Bone Joint Surg Br* 2003;85:380–8.
43. Montori VM, Devereaux PJ, Adhikari NK, et al. Stopping randomized clinical trials early for benefit: a protocol of the study of trial policy of interim truncation-2 (STOPIT-2). *Trials* 2009;10:49.
44. Fine J, Gray R. A proportional hazards model for the sub-distribution of a competing risk. *J Am Stat Assoc* 1999;94:496-509.

FIGURE LEGEND

Figure 1: Expertise-Based Randomized Controlled Trial
An expertise-based randomized controlled trial design randomizes participants to surgeons with expertise in surgery A or to surgeons with expertise in surgery B.

Figure 2: Schedule of Events
** Complete forms when and/or if applicable*

Figure 3: Strategies to Enhance Follow-Up Rates

Hip Fracture Evaluation with Alternatives of Total Hip Arthroplasty versus Hemi-Arthroplasty (HEALTH): Protocol for a Multi-Centre Randomized Trial

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ABSTRACT

Introduction

Hip fractures are a leading cause of mortality and disability worldwide and the number of hip fractures is expected to rise to over 6 million per year by 2050. The optimal approach for the surgical management of displaced femoral neck fractures remains unknown. Current evidence suggests the use of arthroplasty; however, there is lack of evidence regarding whether patients with displaced femoral neck fractures experience better outcomes with total hip arthroplasty (THA) or hemi-arthroplasty (HA). The HEALTH trial compares outcomes following THA versus HA in patients 50 years of age or older with displaced femoral neck fractures.

Methods and Analysis

HEALTH is a multi-centre, randomized controlled trial where 1,434 patients 50 years of age or older with displaced femoral neck fractures from international sites, are randomized to receive either THA or HA. Exclusion criteria include associated major injuries of the lower extremity, hip infection(s) and a history of frank dementia. The primary outcome is unplanned secondary procedures and the secondary outcomes include functional outcomes, patient quality of life, mortality, and hip-related complications – both within two years of the initial surgery. We are using minimization to ensure balance between intervention groups for the following factors: age, pre-fracture living, pre-fracture functional status, American Society for Anesthesiologists (ASA) Class, and centre number. Data analysts and the HEALTH Steering Committee are blinded to surgical allocation throughout the trial. Outcome analysis will be performed using a Chi-square test (or Fisher's exact test) and Cox proportional hazards modeling estimate. All results will be presented with 95% confidence intervals.

Ethics and Dissemination

The HEALTH trial has received local and McMaster University Research Ethics Board (REB) approval (REB#: 06-151). Results from the primary manuscript will be disseminated through publications in academic journals and presentations at relevant orthopaedic conferences.

Trial Registration

The HEALTH trial is registered with clinicaltrials.gov (NCT00556842).

STRENGTHS AND LIMITATIONS

Strengths

- This study has a large sample size of 1,434 patients in order to detect small but important differences in outcomes.
- We are utilizing an expertise-based randomized controlled trial design to help to eliminate differential performance and differential outcome assessments and reduce crossovers and ethical concerns associated with randomization.
- The study has stringent methodological safeguards against bias including: use of a centralized randomization system; blinding data analysts and the Steering Committee; standardization and documentation; use of strategies to limit loss to follow up; and adjudication of trial events by an independent Central Adjudication Committee.

Limitation

- Surgeons and patients cannot be blinded to the surgical arms, leaving the assessment of outcomes and decisions to re-operate vulnerable to bias.
- We do not allow family members and friends to answer questionnaires on behalf of cognitively impaired patients, so some secondary outcomes will only apply to patients who are not cognitively impaired.
- The two year follow up limits the study to shorter-term outcomes.

INTRODUCTION

The number of hip fractures globally is expected to rise to over 6 million by the year 2050.[1, 2] Due to projected aging of the population, 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.[3-5] By the year 2040, the estimated annual health care costs associated with hip fractures will reach $9.8 billion in the United States and $650 million in Canada.[6] 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.[7] In the elderly, hip fractures are associated with a 30% mortality rate at 1 year post-injury and profound temporary,[8] and often permanent, impairment of independence and quality of life.[9, 10] Worldwide, 4.5 million people are disabled from hip fractures yearly with the number of persons living with disability expected to increase to 21 million in the next 40 years.[3, 5, 11] The disability adjusted life-years lost as a result of hip fractures ranks in the top 10 of all causes of global disability.[3]

Inconclusive Clinical Evidence

Femoral neck fractures may be either non-displaced (i.e., very little separation at the fracture site, about one third of femoral neck fractures) or displaced (i.e., greater separation at the fracture site, about two thirds of femoral neck fractures). Orthopaedic surgeons often treat non-displaced fractures with internal fixation and displaced fractures with arthroplasty, which is also known as joint replacement.

We conducted a comprehensive literature search to identify all studies investigating total hip arthroplasty (THA; involves replacing the femoral head and the acetabulum) compared to hemi-arthroplasty (HA; involves replacing the femoral head only) for displaced femoral neck fractures. We identified a recent meta-analysis of 14 studies (N=1,890 patients).[12] This meta-analysis demonstrated a lower risk of re-operation after THA compared with HA (relative risk 0.57, 95% CI 0.34 to 0.96); however, this effect was mainly driven by randomized controlled trials (RCTs) without concealed treatment allocation. THA consistently resulted in better hip function (Harris Hip Score, weighted mean difference 5.4, 95% CI 2.7 to 8.2) after follow-up intervals of 12 to 48 months.[12] We also identified two additional meta-analyses that provide comparisons of THA and HA.[13, 14] Liao et al pooled RCTs of THA (N=403 patients) versus HA (N=425 patients),[13] and found reductions in the risk of secondary procedures and wound infection with THA. Furthermore, Liao et al reported that the mobility rate in THA was better than in HA. Burgers et al performed a meta-analysis of eight RCTs (N=986 patients) that suggested similar rates of secondary procedures,[14] one year mortality, major complications, and minor complications with THA and HA, but large benefits in patient function with THA. Despite the benefits that THA confers regarding functional outcomes, secondary procedures, and infection rates, both meta-analyses reported higher hip dislocation rates with THA.

In a survey of 298 surgeons who were members of the Orthopaedic Trauma Association or affiliated with AO International, 94-96% of surgeons agreed that arthroplasty is the preferred treatment option in patients over 80 years of age with displaced femoral neck fractures.[15] In addition, 73% of surgeons surveyed preferred HA to THA.[15] In summary, current evidence suggests substantial benefits of THA over HA in decreased pain and improved function, but also increased rates of dislocation associated with THA, with similar rates of secondary procedures and mortality with the two procedures. Despite the apparent benefits of THA over HA, surgeons

more often prefer HA to treat displaced femoral neck fractures. Previous trials comparing these two approaches were limited by methodological issues, so the current trial aims to determine the effectiveness of THA compared to HA using a large sample size and high-quality methodology.

Study Objectives

Our primary objective is to assess the impact of THA versus HA on rates of unplanned secondary procedures at two years in individuals with displaced femoral neck fractures.

Secondary objectives are:

1. To examine the effect of THA versus HA 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 THA versus HA on mortality.
3. To evaluate the effect of THA versus HA 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 (e.g. pseudotumor), heterotopic ossification, abductor failure, implant wear and corrosion, osteolysis, neurovascular injury, decreased function, and pain.

METHODS AND ANALYSIS

Overview of Study Design

HEALTH is a multi-centre, concealed RCT of 1,434 elderly patients who have sustained a displaced femoral neck fracture. We are using minimization, a form of randomization, to determine patient allocation. Surgeons across North America, Europe, Australia, and Asia are participating. In conventional surgical hip fracture trials, all surgeons involved in the trial have performed both THA and HA based on the randomization process. HEALTH utilizes an expertise-based randomized trial design that allocates patients to surgeons with expertise in THA or HA (**Figure 1**). Based upon their expertise, surgeons perform either THA or HA. Surgeons who feel confident enough to perform both surgical strategies perform both THA and HA.

Patient Selection

Eligibility Criteria

The inclusion criteria are: 1) Adult men or women aged 50 years and older (with no upper age limit); 2) Fracture of the femoral neck confirmed with antero-posterior (AP) and lateral radiographs or computed tomography (CT) 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 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); and 10) Assurance that surgeons with expertise in both THA and HA are available to perform surgery.

The exclusion criteria are: 1) Patient not suitable for HA (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 (e.g. 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 (e.g. 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 two years); 7) Likely problems, in the judgment of the investigators, with maintaining follow-up (e.g. patients with no fixed address, report a plan to move out of town, alcohol abuse issues, or intellectually challenged patients without adequate family support); and 8) Patients whose fracture occurred as a result of an act of violence.

Patient Recruitment and Screening

The first patient was randomized into the vanguard phase of this trial on 21 January 2009. After a brief pause in enrollment between the vanguard and definitive phase, the first definitive patient was randomized on 8 October 2013. Enrollment is ongoing at the time pf publication and is expected to be completed by December 2016. All patients presenting to participating surgeons with a diagnosed femoral neck fracture amenable to arthroplasty are screened for participation in the HEALTH trial. Such patients are classified as: 1) Excluded (if they do not meet the eligibility criteria); 2) Missed (presumed eligible but missed due to error or staff availability); or 3) Included (eligible and randomized). Study personnel obtain informed consent from all eligible patients. If a patient lacks capacity and is deemed unable to consent, study personnel may obtain informed consent from the patient's legally authorized representative and assent from the patient.

Randomization

We are ensuring concealment of allocation by using a centralized 24-hour computerized randomization system that will allow internet-based randomization. Patients are the unit of randomization. To protect against prognostic imbalance between groups, we are using minimization to ensure balance between intervention groups for several patient factors. The minimization approach takes into account each pre-identified prognostic variable and sums over the variables to allocate each patient to the treatment that will minimize the differences between groups for those prognostic variables. Unlike stratified randomization, minimization works toward minimizing the total imbalance for all factors together instead of considering mutually exclusive subgroups (strata).[16] Based on our international survey of surgeons,[15] and current evidence,[17] we are minimizing for the following prognostic factors: 1) Age (i.e., 50 to 80 years or greater than 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); and 5) Participating centre.

Study Interventions

Total Hip Arthroplasty

In the THA group, we are not including minimally invasive THA (i.e., 2 incision approaches) or hinged prostheses or capture cups. To optimize feasibility and applicability of results, we did not standardize the surgical approach including the use of cemented components, the implant manufacturer, or femoral head size. We are documenting the manufacturer, implant material, and bearing surface of the implant.

Hemi-Arthroplasty

Surgeons are to use modern implants for HA excluding non-modular, non-canal filling unipolar implants such as Moore's and Thompson's prostheses. We did not standardize the choice of modular unipolar versus bipolar HA nor whether implants are inserted with cement or with a press-fit design. We are documenting the manufacturer, implant material, and bearing surface of the implant.

Standardization of Procedures and Peri-Operative Care

To ensure similar peri-operative regimens, we recommend that participating centres standardize key aspects of pre- and post-operative care. For pre-operative care, we recommend standardization of the following: (1) Pre-operative antibiotic prophylaxis (e.g. cephalosporins or equivalent coverage); (2) Thromboprophylaxis (e.g. oral anticoagulation drugs, thromboembolic deterrent 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)); and (3) Medical consultation to optimize condition prior to surgery. For post-operative care, we recommend standardization of the following: (1) Antibiotic prophylaxis (e.g. 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 are weightbearing as tolerated, and then advanced according to the attending surgeon's best judgment; (4) 600 mg calcium by mouth daily and 1000 IU vitamin D per day (provided there are no contraindications) and further investigation and treatment of osteoporosis as recommended by a local osteoporosis expert/consultant; and (5) Appropriate nutritional assessment with administration of oral micronutrient feeds as needed. Due to a lack of evidence favouring a particular approach, we are recording but did not standardize the following: (1) Use of pre-operative traction; (2) Surgical delay; (3) Type of anesthetic (i.e., general or regional); and (4) Patient participation in physiotherapy and rehabilitation.

Study Outcomes

Primary Study Outcome

The primary outcome is any unplanned secondary procedure within 2 years of the initial hip 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**).

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

Specific unplanned secondary procedures	Classification of the reason for secondary

include:	procedures is as follows:
• Closed reduction of hip dislocation • Open reduction of hip dislocation • Open reduction of fracture • Soft tissue procedure • Insertion of antibiotic spacer • Full implant exchange • Partial implant exchange – stem only • Partial implant exchange - head only • Partial implant exchange - liner only • Partial implant exchange - head and liner • Partial implant exchange – acetabular component only • Partial implant exchange – acetabular component and head • Implant adjustment – re-orientation of the stem • Implant adjustment – re-orientation of the acetabulum component • Implant removal with no replacement • Excision heterotopic ossification • Supplementary fixation	• Treat a peri-prosthetic fracture • Treat hip instability or dislocation • Treat infection – superficial • Treat infection – deep • Treat wound necrosis • Treat another wound healing problem • Remove heterotopic ossification • Manage abductor failure • Manage another soft tissue problem (i.e. pseudotumor) • Correct implant failure –loosening or subsidence • Correct implant failure - breakage • Treat implant wear • Treat osteolysis • Treat implant corrosion • Improve function • Relieve pain

Secondary Study Outcomes

Secondary outcomes include: 1) Functional outcome and quality of life measured using self-administered and interview-administered questionnaires. 2) The effect of THA versus HA on mortality; 3) 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 (e.g. pseudotumor), heterotopic ossification, abductor failure, implant wear and corrosion, osteolysis, neurovascular injury, decreased function, or pain.

Functional outcome and quality of life are measured using self-administered and interview-administered questionnaires. Functional outcome questionnaires include a generic health status measurement instrument (SF-12),[18] a hip function and pain questionnaire (WOMAC),[19] a health outcome measure (EQ-5D),[20] and a functional mobility test (TUG).[21]

The SF-12 questionnaire 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). The instrument has been extensively validated and has demonstrated good construct validity, high internal

consistency, and high test-retest reliability.[22] It is frequently used in orthopaedics for evaluating fracture outcomes.

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.[19] It is a valid, reliable and responsive measure of outcome, and has been used in several studies involving a wide range of lower extremity conditions.[23]

The EQ-5D is a comprehensive, compact health status classification and health state preference system.[20] This questionnaire is widely used and has demonstrated validity and sensitivity in many populations.[20, 22] The EQ-5D is generalizable, as it is widely used in Europe, and will be useful for our definitive trial in which we will be including international sites.

The timed up and go test (TUG) involves observing the patient and documenting the time,[21] in seconds, it takes for the patient to rise from a standard arm chair, walk to a line on the floor 3 metres away, turn, return, ands sit down again. The TUG has been used in many clinical contexts including orthopaedics,[24] rheumatology,[25] and predicting geriatric falls.[26]

Adjudication of Study Events

The HEALTH Central Adjudication Committee (CAC) is comprised of five orthopaedic surgeons who specialize in hip surgery and have expertise in research methodology and experience with clinical trials. The CAC are reviewing: 1) Cases where fracture eligibility is in doubt; 2) Post-operative x-rays to assess the technical placement of prostheses; 3) All reported secondary procedures and fracture-related complications to determine if a secondary procedure and/or fracture-related complication meeting study criteria has occurred; and 4) Cases of mortality to confirm the cause of death. All centres submit digital x-rays to the HEALTH Methods Centre. We post all relevant patient records devoid of personal identifiers (i.e., case report forms and x-rays) on a specially designed, password-protected website for study adjudication. Adjudication occurs after patients have completed their two year follow-up. Any disagreements among the CAC members are resolved during conference calls. All decisions made by the Committee are final.

Study Follow Up

All patients are followed for a period of two years. At each follow up interval, patients' health status and outcomes are recorded. In addition, at the 2-year follow-up visit, the surgeon documents any secondary procedure that may be planned for the patient. **Figure 2** shows the schedule of events and assessments at each time point.

Our choice of a 2-year follow-up period is dictated by two factors. First, previous studies have reported that 75% of revision surgeries occur before 12 months for patients treated with arthroplasty for displaced femoral neck fractures.[27] Thus, we can expect that the majority of revision surgeries will occur within 2 years. Since increasing follow-up to beyond 2 years will yield little additional information on secondary procedure rates, efficient use of resources dictates a 2-year follow-up. Second, a full 2 years of follow-up will provide sufficient time to assess any potential gains in function and quality of life afforded by either surgical alternative.

Protecting Against Sources of Bias

Blinding

While surgeons, patients, and outcome assessors cannot be blinded to the surgical arms (i.e., THA or HA), data analysts and the Steering Committee will remain blinded throughout the trial. Secondary procedures, the primary outcome, are objective and lack of blinding introduces minimal threats to validity. Additionally, the HEALTH trial design eliminates differential expertise bias by establishing a minimal threshold for experience, as well as ensuring that all surgeons performing either THA or HA are dedicated to and have sufficient expertise with the procedure.

Surgeon Expertise

Surgeons participating in the HEALTH trial are asked to meet both of the following two criteria for expertise for either THA or HA: 1) Perform at least 50 procedures (either THA or HA) in their career (including residency experience in which they assumed responsibility for the procedure), and 2) Perform at least 5 procedures per year. Surgeons who meet the threshold for both THA and HA will perform both procedures, if no overwhelming bias in favour of one procedure is evident. A surgeon is 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 the threshold expertise criteria and must be present in the operating room for the critical aspects of the procedure (**Table 2**). Our decision to set 50 procedures as the threshold for experience is based upon previous studies examining learning curves and respective outcomes in patients undergoing THA.[28-30] Our survey of surgeons who are members of the Orthopaedic Trauma Association (OTA) or European AO International trauma centres suggests that the threshold of HA is likely similar or slightly lower, given the perception of increased difficulty of THA.

Devereaux and colleagues have outlined the advantages of this trial design,[31] 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 over the other.
2. Differential performance, co-intervention, data collection, and outcome assessment are less likely than in conventional RCT.

With this approach, ethical concerns are reduced because all surgeries are conducted by surgeons with expertise and conviction concerning the procedures.[31]

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

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

Maximizing Patient Retention

Previous trials in hip fracture surgery have lost up to 50% of patients to follow-up.[15] To avoid this problem, the strategies outlined in **Figure 3** are used to minimize loss to follow-up. We have successfully used the majority of these strategies to maximize follow-up in other multi-centre studies. Key features of this strategy include: 1) excluding individuals who are likely to present problems with follow-up; 2) prior to hospital discharge, in addition to proving their own contact information, each patient provides the name and address of alternate contacts who are likely to be aware of the patient's whereabouts; 3) patients receive a reminder for their next follow up visit from the clinical research coordinator; and 4) follow-up visits coincide with standard fracture clinic visits. Additionally, patients can complete some study visits over the phone provided no radiographs are required.

Minimizing Co-Interventions and Contamination

Any patients who cross over from one treatment group to the other will be analyzed in the group to which they were allocated, maintaining the intention to treat approach of the analysis. Surgical co-interventions such as general, neurosurgical, or orthopaedic procedures performed in addition to the arthroplasty procedure, have the potential to confound outcomes. The standardization of key aspects of pre-operative and post-operative care, together with the expertise-based trial design will minimize the use of co-interventions in study patients. Clinical sites record the details of any major additional procedures performed, as well as the use of medications that affect bone, such as bisphosphonates, vitamin D, calcium, hormone replacement therapy, selective estrogen receptor modulators, calcitonin, and anabolic steroid therapy.

Maximizing Protocol Adherence

Given the inherent variability in practice patterns among orthopaedic surgeons, we believe it is important to ensure that surgeons adhere as closely as possible to the surgical management protocol. The feasibility of this large study involving multiple centres further depends upon minimal changes from current practice. Our study protocol closely follows currently accepted practice in the management of patients with femoral neck fractures. We therefore anticipate high compliance with our protocol.

Statistical Plan

Sample Size Determination

The choice of sample size is based upon a comparison of THA versus HA for the primary outcome (unplanned secondary procedures). 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 [14]. 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**) [14, 32-36].

Table 3a: Sample Size Calculations Comparing Total Hip Arthroplasty (THA) and Hemi-Arthroplasty (HA)

Studies included in a meta-analysis comparing THA with HA for the outcome of reoperation at one year

Study	THA Reoperation Rate	HA Reoperation Rate
van den Bekerom 2010 [32]	5/110 (4.5%)	1/136 (0.7%)
Baker 2006 [33]	4/36 (11.1%)	2/39 (5.1%)
Blomfeldt 2007 [34]	4/56 (7.1%)	3/57 (5.3%)
Keating 2006 [35]	6/63 (9.5%)	5/64 (7.8%)
Macaulay 2008 [36]	1/16 (6.25)	0/23 (0%)

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)

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.[37] 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 corresponding 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 [unpublished data]. 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.

Table 3b: Sample Size Calculations Comparing Total Hip Arthroplasty (THA) and Hemi-Arthroplasty (HA)

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

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

RRR = Relative Risk Reduction

For the secondary outcomes, an important difference in SF-12 is considered to correspond to a moderate effect as reported by Cohen as well as a minimally important difference in the SF-12 as reported by Ware.[38, 39] 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,[40] 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.[41] In this study, at least 90 patients (45 per group) would be required to detect this difference (alpha level=0.05, beta=0.20, σ =15). Previous studies have found a standard deviation of 0.20 for the EQ-5D.[42] 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.

Primary Analyses

All outcome analyses will be performed by an intention to treat approach. To evaluate the effect of THA versus HA on time to unplanned 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); and 5) Participating centre. Results

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

Secondary Analyses

As a secondary analysis, we will adjust for additional baseline factors when examining the effect of THA versus HA on time to unplanned secondary procedures (the primary outcome). This will be a Cox proportional hazards model which will include the same variables that are included in our primary analysis, and additionally adjusting for 1) Gender, 2) Surgical approach, and 3) Head size, by including these as independent variables. Results will be reported as hazard ratios with 95% confidence intervals.

A generalized linear model will estimate the effect of THA versus HA 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 (50 to 80 years or greater than 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); and 5) Participating centre.

Cox proportional hazards modeling will estimate the relative effect of THA versus HA 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.

Interim Analyses

The approach to interim analyses is guided by a desire to avoid spuriously inflated estimates of treatment effect.[43] 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. 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.

Data Management

The Case Report Forms (CRFs) are the primary data collection tool for the study. An Electronic Data Capture system (iDataFax) is being used to submit data to the Methods Centre located at McMaster University. Upon receipt of the data, the personnel at the Methods Centre make a visual check of the data and they query all missing data, implausible data, and inconsistencies.

Sensitivity Analyses

We will perform some sensitivity analyses to assess the robustness of the primary results. First, we will perform a competing risk analysis using Fine and Gray method to account for death as a competing risk.[44] Second, we will use the random-effects analysis with a centre as a random-effect to account for the possibility of the centre effect or clustering within a centre. Lastly, based on the pilot results we anticipate some cross-overs during the trial—we will monitor these and perform some sensitivity analysis to assess their impact. All analyses will be performed using SAS 9.2 (Cary, NC).

Missing Data

Patients who are lost or withdrawn from the study prior to full 24 month follow-up will be censored at their last visit where evaluation of the primary endpoint was completed.

Data Monitoring Committee

The purpose of the Data Monitoring Committee (DMC) is to advise the HEALTH Investigators regarding the continuing safety of study participants. The DMC consists of the Chair, who is an orthopaedic surgeon, one biostatistician, and two additional orthopaedic surgeons. All members are independent of the trial investigators, and have neither financial nor scientific conflicts of interest with the trial. Further details regarding the DMC can be found in the DMC Charter, available from the corresponding author.

ETHICAL CONSIDERATIONS

All patients (or their legally authorized representative) included in this study will sign a consent form that describes this study and provides sufficient information for patients to make an informed decision about their participation. All participating centres will submit the consent form with the protocol for review and approval by their local research ethics board (REB) or institutional review board (IRB) for the study. Centres will obtain written consent from every patient, using the REB/IRB-approved consent form, before that patient undergoes any study procedure. Any amendments to the study protocol which may affect the conduct of the study, or the potential safety of or benefits to patients will require a formal amendment to the protocol requiring approval by McMaster University's REB and local research ethics boards for clinical sites. Any protocol amendments will be communicated to investigators, REB/IRB, trial participants, and trial registries as necessary.

Information about study patients will be kept confidential and will be managed in accordance with the following rules: (1) All study-related information will be stored securely at the clinical site; (2) All study patient information will be stored in locked file cabinets and accessible only to study personnel; (3) All CRFs will be identified only by a coded patient number and initials; (4) All records that contain patient names, or other identifying information, will be stored separately from the study records that are identified only by the coded patient number and initials; and (5) All local databases will be password protected.

DISSEMINATION

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

Only the Methods Centre will have access to the full trial dataset. Data for the primary publication will be analyzed exclusively by the Methods Centre. Requests for access to the full trial dataset for secondary publications are encouraged and can be initiated through a written request to Methods Centre personnel.

DISCUSSION

Previous orthopaedic trials have addressed the effect of THA versus HA on patient outcomes; however, the trials conducted to date are limited by small sample sizes, lack of concealed randomization, differential expertise biases,[13] and most were single centre initiatives that lacked sufficient power to inform surgical practice. Orthopaedic surgeons appear to currently favor HA, although current evidence suggests superior patient-important outcomes with THA.[14, 31] The HEALTH trial will aim to resolve these controversies by establishing the effectiveness of each method of arthroplasty. This will have important clinical implications as each treatment is easily applicable and already in use in orthopaedic practice.

The HEALTH trial will address and overcome many of the limitations of previous orthopaedic hip fracture trials. Firstly, the study sample size of 1,434 patients is sufficient to detect small, but important differences in outcomes, and will ensure that our study objectives are met. Secondly, using an expertise-based RCT has many advantages over traditional orthopaedic hip studies, including eliminating differential performance and differential outcome assessment and reducing the number of crossovers and ethical concerns associated with randomization.[13] Furthermore, the HEALTH trial has stringent methodological safeguards against bias including: the use of a centralized system to randomize patients; blinding data analysts and the Steering Committee; standardization and documentation of pre-operative care, peri-operative care and post-operative care; the use of strategies to limit loss to follow up; and adjudication of trial events by an independent Central Adjudication Committee.

A key limitation of the HEALTH trial is that surgeons and patients cannot be blinded to the surgical arms. This leaves the assessment of outcomes and decisions to re-operate vulnerable to bias. We have limited this bias by using an objective primary outcome (unplanned secondary procedures) and by centrally adjudicating all primary outcome events using a group of independent orthopaedic surgeons. Additionally, we do not allow family members or friends to answer questionnaires on behalf of cognitively impaired patients, so some secondary outcomes will only apply to patients who are not cognitively impaired. Our trial is limited to shorter-term outcomes; up to two years following the initial surgery. Therefore our results may not apply when considering longer term outcomes.

The results of the HEALTH trial will be an important contribution to orthopaedic surgical literature and likely lead to changes in orthopaedic practice. Identifying the optimal approach to arthroplasty has the potential to improve the lives of hundreds of thousands of patients and to reduce the economic burden associated with hip fractures. If this trial shows that one approach is superior to the other, it will revolutionize the treatment of hip fractures globally, and may potentially lead to the establishment of new clinical guidelines for treatment of displaced femoral neck fractures. In addition to the clinical impact, the HEALTH trial also has the potential to impact orthopaedic trial conduct. With this trial we will build collaborative relationships among

countries and between clinical centres. This trial will also contribute to challenging the dogma that surgical trials are doomed to small single centre initiatives.

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COMPETING INTEREST STATEMENT

The authors have no competing interests to report.

REFERENCES

1. Cooper C, Campion G, Melton LJ, 3rd. Hip fractures in the elderly: a world-wide projection. *Osteoporos Int* 1992;2:285–9.
2. Dhanwal DK, Dennison EM, Harvey NC, et al. Epidemiology of hip fracture: worldwide geographic variation. *Indian J Orthop* 2011;45(1):15–22.
3. Johnell O, Kanis JA. An estimate of the worldwide prevalence, mortality and disability associated with hip fracture. *Osteoporos Int* 2004;15:897–902.
4. Iorio R, Schwartz B, Macaulay W, et al. Surgical treatment of displaced femoral neck fractures in the elderly: a survey of the American association of hip and knee surgeons. *Arthrop* 2006;21(8):1124-33.
5. Cummings SR, Rubin SM, Black D. The future of hip fractures in the United States. Numbers, costs, and potential effects of postmenopausal estrogen. *Clin Orthop Relat Res* 1990;252:163–6.
6. Papadimitropoulos EA, Coyte PC, Josse RG, et al. Current and projected rates of hip fracture in Canada. *CMAJ* 1997;157:1357-63.
7. AAOS urges hip fracture reform. American Academy of Orthopaedic Surgeons Bulletin 1999;47.
8. Moran CG, Wenn RT, Sikand M, et al. Early mortality after hip fracture: is delay before surgery important? *J Bone Joint Surg* 2005;87:483-89.
9. Jongjit J, Komsopapong L, Songjakkaew P, et al. Health-related quality of life after hip fracture in the elderly community-dwelling. *Southeast Asian J Trop Med Public Health* 2003;34:670-4.
10. Carrière G. Hip fracture outcomes in the household population. *Health Rep* 2007;18(4):37-42.
11. Cooper C, Campion G, Melton LJ. Hip fractures in the elderly: a world-wide projection. *Osteoporos Int* 1992;2:285–9.
12. Hopley C, Stengel D, Ekkernkamp A, et al. Primary total hip arthroplasty versus hemiarthroplasty for displaced intracapsular hip fractures in older patients: systematic review. *BMJ* 2010;340:c2332.
13. Liao L, Zhao Jm, Su W, et al. A meta-analysis of total hip arthroplasty and hemiarthroplasty outcomes for displaced femoral neck fractures. *Arch Orthop Trauma Surg* 2012;132(7):1021-9.
14. Burgers PTPW, Van Geene AR, Van den Bekerom MPJ, et al. Total hip arthroplasty versus hemiarthroplasty for displaced femoral neck fractures in the healthy elderly: a meta-analysis and systematic review of randomized trials. *Int Orthop* 2012;36:1549-60.
15. Bhandari M, Devereaux PJ, Tornetta P 3rd, et al. Operative management of displaced femoral neck fractures in elderly patients. An international survey. J Bone Joint Surg Am 2005;87:2122-30.
16. Pandis N. Randomization. Part 2: Minimization. *Am J Orthod Dentofacial Orthop* 2011;140(6):902-4.
17. Gillespie WJ. Extracts from "clinical evidence": hip fracture. *BMJ* 2001;322:968-75.
18. McHorney CA, Ware JE Jr, Rogers W, et al. The validity and relative precision of MOS short- and long-form health status scales and Dartmouth COOP charts. Results from the medical outcomes study. *Med Care* 1992;30(5 suppl):MS253-65.
19. Bellamy N, Buchanan WW, Goldsmith CH, et al. Validation of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol* 1988;15:1833-40.

20. Brooks R, Rabin RE, de Charro F, (Eds). The Measurement and Valuation of Health Status Using EQ-5D: A European Perspective. Dordrecht, The Netherlands: Kulwer Academic Publishers 2003.
21. Podsiadlo D, Richardson S. The timed 'up and go' test: a test of basic functional mobility for frail elderly persons. *J of Am Geri Soc* 1991;39(2):142-8.
22. Ware JE, Kosinski M, Keller SD. A 12-item short-form health survey: construction of scales and preliminary tests of reliability and validity. *Med Care* 1996;34:220-33.
23. Dattani R, Slobogean GP, O'Brien PJ, et al. Psychometric analysis of measuring functional outcomes in tibial plateau fractures using the Short Form 36 (SF-36), Short Musculoskeletal Function Assessment (SMFA) and the Western Ontario McMaster Osteoarthritis (WOMAC) questionnaires. *Injury* 2013;44(6):825-9.
24. Laflamme GY, Rouleau DM, Leduc S, et al. The Timed Up and Go test is an early predictor of functional outcome after hemiarthroplasty for femoral neck fracture. J Bone Joint Surg Am. 2012;94(13):1175-9.
25. McMeeken J, Stillman B, Story I, et al. The effects of knee extensor and flexor muscle training on the timed-up-and-go test in individuals with rheumatoid arthritis. *Physiother Res Int* 1999;4(1):55-67.
26. Shumway-Cook A, Brauer S, Woollacott M. Predicting the probability for falls in community-dwelling older adults using the Timed Up & Go Test. *Phys Ther* 2000;80(9):896-903.
27. Ravikumar KJ, Marsh G. Internal fixation versus hemiarthroplasty versus total hip arthroplasty for displaced subcapital fractures of femur -13 year results of a prospective randomised study. *Injury* 2000;31:793-7.
28. Callaghan JJ, Heekin RD, Savory CG, et al. Evaluation of the learning curve associated with uncemented primary porous-coated anatomic total hip arthroplasty. *Clin Orthop Relat Res* 1992;282:132-44.
29. Ellinor N, Lindelof N, Rosendahl E, et al. Prognostic validity of the Timed Up-and-Go test, staff's global judgement and fall history in evaluating fall risk in residential care facilities. *Age Ageing* 2008;37:442-8.
30. Katz JN, Losina E, Barrett J, et al. Association between hospital and surgeon procedure volume and outcomes of total hip replacement in the United States medicare population. *J Bone Joint Surg Am* 2001;83-A(11):1622-9.
31. Devereaux PJ, Bhandari M, Clarke M, et al. Need for expertise based randomised controlled trials. BMJ 2005;330:88-91.
32. van den Bekerom MP, Hilverdink EF, Sierevelt IN, et al. A comparison of hemiarthroplasty with total hip replacement for displaced intracapsular fracture of the femoral neck: a randomised controlled multicentre trial in patients aged 70 years and over. J Bone Joint Surg Br. 2010;92(10):1422-8.
33. Baker RP, Squires B, Gargan MF, et al. Total hip arthroplasty and hemiarthroplasty in mobile, independent patients with a displaced intracapsular fracture of the femoral neck. A randomized, controlled trial. J Bone Joint Surg Am. 2006;88(12):2583-9.
34. Blomfeldt R, Törnkvist H, Eriksson K, et al. A randomised controlled trial comparing bipolar hemiarthroplasty with total hip replacement for displaced intracapsular fractures of the femoral neck in elderly patients. J Bone Joint Surg Br. 2007;89(2):160-5.

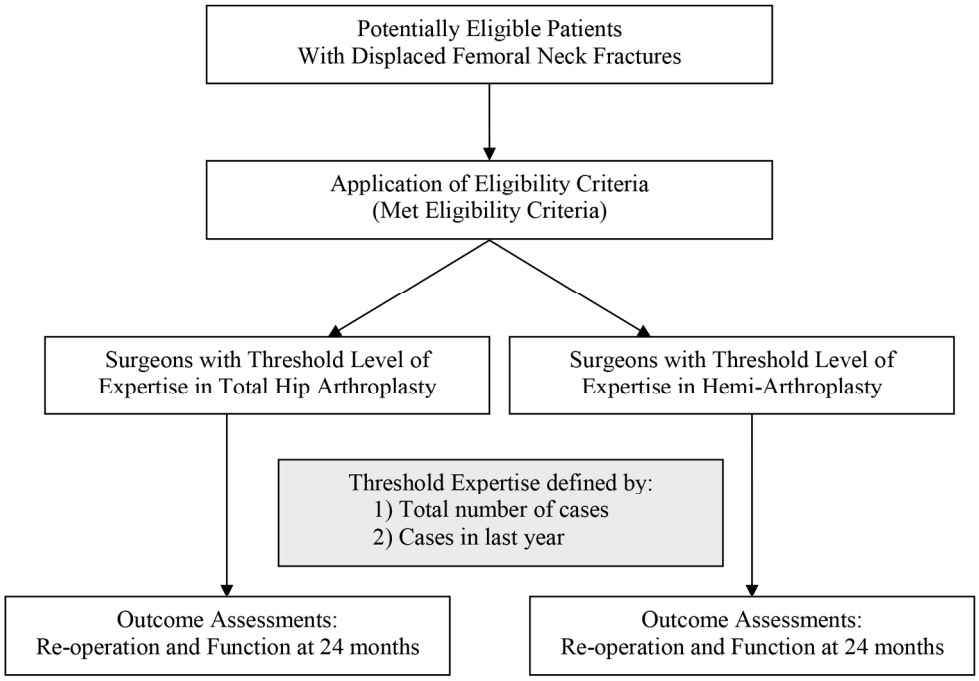
35. Keating JF, Grant A, Masson M, et al. Displaced intracapsular hip fractures in fit, older people: a randomised comparison of reduction and fixation, bipolar hemiarthroplasty and total hip arthroplasty. *Health Technol Assess* 2005:9;1-65.
36. Macaulay W, Nellans KW, Garvin KL, et al. Prospective randomized clinical trial comparing hemiarthroplasty to total hip arthroplasty in the treatment of displaced femoral neck fractures. J Arthroplasty. 2008;23(6 Suppl 1):2-8.
37. Collett D. Modelling Survival Data in Medical Research. London, UK: Chapman & Hall 1994.
38. Cohen J. Statistical Power Analysis For The Behavioral Sciences. 2nd editions. Hillsdale, NJ: Lawrence Erlbaum Associates 1988.
39. Ware JE, Sherbourne CD. The MOS 36-item short form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30:473-83.
40. Jaglal S, Lakhani Z, Schatzker J. Reliability, validity, and responsiveness of the lower extremity measure for patients with a hip fracture. *J Bone Joint Surg Am* 2000;82:955-62.
41. Tubach F, Ravaud P, Baron G, et al. Evaluation of clinically relevant changes in patient reported outcomes in knee and hip osteoarthritis: The minimal clinically important improvement. *Ann Rheum Dis* 2005;64:29-33.
42. Tidermark J, Ponzer S, Svensson O, et al. Internal fixation compared with total hip replacement for displaced femoral neck fractures in the elderly: a randomised, controlled trial. *J Bone Joint Surg Br* 2003;85:380–8.
43. Montori VM, Devereaux PJ, Adhikari NK, et al. Stopping randomized clinical trials early for benefit: a protocol of the study of trial policy of interim truncation-2 (STOPIT-2). *Trials* 2009;10:49.
44. Fine J, Gray R. A proportional hazards model for the sub-distribution of a competing risk. *J Am Stat Assoc* 1999;94:496-509.

FIGURE LEGEND

Figure 1: Expertise-Based Randomized Controlled Trial
An expertise-based randomized controlled trial design randomizes participants to surgeons with expertise in surgery A or to surgeons with expertise in surgery B.

Figure 2: Schedule of Events
** Complete forms when and/or if applicable*

Figure 3: Strategies to Enhance Follow-Up Rates



172x121mm (300 x 300 DPI)

Radiographs & Event Forms	Pre-Surgery			Surgery	Post Surgery								
	Screening	Enrollment	Baseline	(Day 0)	≤ 48 hrs Post Surgery	Discharge	1 wk	10 wk	6 mo	9 mo	12 mo	18 mo	24 mo
Patient Contact		•			•	•	•	•	•	•	•	•	•
Radiographs			•		•			•			•		•
Screening	•												
Informed Consent		•											
Randomization		•											
Baseline			•										
Surgical Report				•									
Post-Op Care					•								
Clinic or Telephone Follow-Up							•	•	•	•	•	•	•
Secondary Procedure					*		*	*	*	*	*	*	*
Adverse Event				*	*		*	*	*	*	*	*	*
Timed Up and Go								•	•		•		•
SF-12							•	•	•	•	•	•	•
WOMAC							•	•	•	•	•	•	•
EQ-5D							•	•	•	•	•	•	•
Missed Follow-Up						*	*	*	*	*	*	*	
Early W/D						*	*	*	*	*	*	*	*

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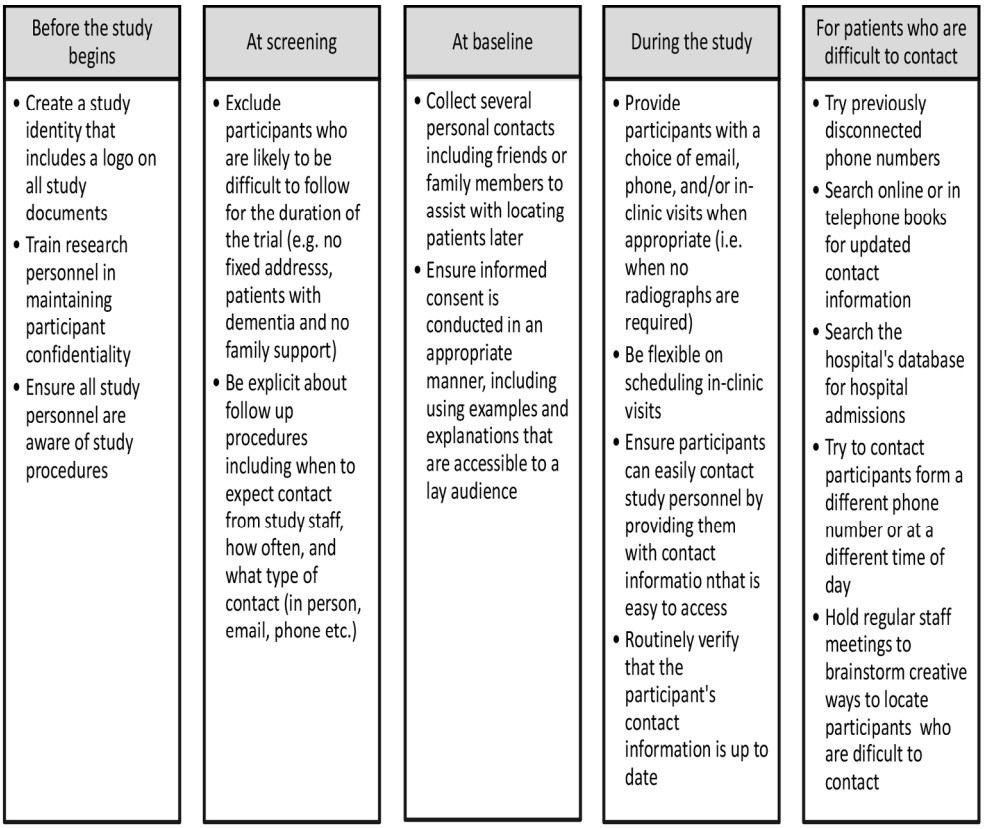

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	1-22
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	20
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	20-22
	5b	Name and contact information for the trial sponsor	N/A
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	20
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	14-15, 20-22

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	4-5
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4-5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5-6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	11
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9-10

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11-13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	11
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6-7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6-7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6-7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9-10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8-9
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	14
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12-14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14-15
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	14
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	7-9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	15

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
	31b	Authorship eligibility guidelines and any intended use of professional writers	20
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.