Fixation Using Alternative Implants for the Treatment of Hip Fractures (FAITH-2)

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Fixation using Alternative Implants for the Treatment of Hip Fractures (FAITH-2):

A Multi-Centre 2x2 Factorial Randomized Trial Comparing Sliding Hip Screws versus Cancellous Screws AND Vitamin D versus Placebo on Patient Important Outcomes and Quality of Life in the Treatment of Young Adult (18-60) Femoral Neck Fractures

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FAITH-2 PROTOCOL

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Explanation
ADL	Activities of Daily Living
AE	Adverse Event
CAC	Central Adjudication Committee
CRF	Case Report Form
DSMC	Data Safety and Monitoring Committee
EDC	Electronic Data Capture
FAITH	Fixation using Alternative Implants for the Treatment of Hip Fractures
HOS	Hip Outcome Score
HRQL	Health-Related Quality of Life
IU	International Units
MRI	Magnetic Resonance Imaging
nmol/L	Nanomole/Litre
PHI	Personal Health Information
RCT	Randomized Controlled Trial
REB	Research Ethics Board
RRR	Relative Risk Reduction
SAE	Serious Adverse Event
SF-12	Short Form-12
SHS	Sliding Hip Screw

STUDY SUMMARY

Title	**F**ixation using **A**lternative **I**mplants for the **T**reatment of **H**ip Fractures (FAITH-2): A Multi-Centre 2x2 Factorial Randomized Trial Comparing Sliding Hip Screws versus Cancellous Screws AND Vitamin D versus Placebo on Patient Important Outcomes and Quality of Life in the Treatment of Young Adult (18-60) Femoral Neck Fractures
Short Title	FAITH-2
Methodology	Concealed 2x2 factorial randomized controlled trial
Clinical Sites	Multiple international clinical sites
Primary Objective	The primary objective is to assess the impact of surgical implant (sliding hip screws versus cancellous screw fixation) *AND* nutritional supplementation (vitamin D versus placebo) on a composite of patient important outcomes during the 12 month post-surgery follow-up period. The composite of patient important outcomes includes: re-operation, femoral head osteonecrosis, severe femoral neck malunion, and nonunion.
Secondary Objectives	To assess the impact of surgical implant (sliding hip screw fixation versus cancellous screw fixation) and nutritional supplementation (vitamin D versus placebo) on health-related quality of life and functional outcomes, fracture healing complications, and radiographic fracture healing.
Sample Size	We will recruit a sample size of 808 patients with full follow-up. Based on an anticipated 10% loss to follow-up, 898 patients will need to be enrolled in the FAITH-2 trial.
Diagnosis and Main Inclusion Criteria	Femoral neck fracture in patients between the ages of 18 and 60.
Study Products	Surgical implants: Sliding hip screw versus multiple cancellous screws. Nutritional supplementation: Vitamin D_3 (4,000 International Units/day taken for 6 months) versus placebo taken for 6 months.
Length of Follow-Up	12 months.

1. INTRODUCTION

This document is a protocol for a human research study that seeks to identify a surgical and nutritional strategy to minimize fracture fixation complications and optimize bone health in order to improve patient outcomes following a femoral neck fracture. Using a concealed 2x2 factorial design, this multi-centre randomized controlled trial (RCT) compares two alternative surgical implants (cancellous screws and sliding hip screws (SHS)) *AND* vitamin D supplementation versus placebo for the treatment of femoral neck fractures in young adult patients (aged 18-60). This trial is registered at clinicaltrials.gov (Identifier number: NCT01908751).

1.1 Femoral Neck Fracture in Young Patients

Globally, hip fractures rank in the top 10 of all cause disability adjusted life years lost.[1] Hip fractures predominately affect elderly people, however, it is estimated that over 300,000 hip fractures occur worldwide in patients under the age of 50 annually.[2,3] Unlike other hip fractures, femoral neck fractures are usually associated with a critical vascular injury that impedes local fracture healing and obliterates the blood supply to the femoral head.[4] This occurs because the important blood vessels of the proximal femur are small, fragile, and most vulnerable to injury at the femoral neck (**Figure 1**). Ultimately, this vascular injury is the primary cause of two devastating complications: femoral neck nonunion (the fracture does not heal) and femoral head osteonecrosis (bone death). These fractures in younger aged patients are associated with high complication rates and profound impairments in quality of life and function.

Virtually all patients with a femoral neck fracture require surgical management of their injury. Surgical options include arthroplasty (joint replacement) or internal fixation. Arthroplasty is often a successful treatment for elderly patients because it removes the fractured area, obviating the risk of fracture healing complications. However, the primary limitation of arthroplasty is the finite lifespan of the implant. Consequently, arthroplasty is not usually considered an optimal treatment option for younger patients. In addition, younger patients have higher functional demands for work and recreational activities that are not well tolerated by joint replacements. For example, Swedish Hip Registry data shows that younger patients experience higher failure rates than elderly patients (9-year survival rates 87.6% for patients aged 55 years of age or younger compared to 97.0% for patients aged 75 years and older) demonstrating that a revision joint replacement is frequently required.[5] In addition, revision hip arthroplasty results in worse functional outcomes than primary joint replacements, represent increased morbidity, and may prevent young patients from returning to their pre-injury function.[6] As result, internal fixation is frequently used to manage the majority of femoral neck fractures in younger patients.

1.2 Internal Fixation of Femoral Neck Fractures

Internal fixation is performed for nearly all femoral neck fractures in young patients to allow patient ambulation, promote healing, and preserve the native hip joint. Young adult femoral neck fractures are typically the result of road traffic accidents and other

high-energy traumas. As a result of their high-energy mechanisms, 80% of these fractures are severely displaced; a state in which the fracture ends are widely separated from each other.[7] During internal fixation surgery, the fracture ends are put together and a metal implant is inserted into the bone to secure the fracture. Unfortunately, complications following internal fixation are common and include femoral head osteonecrosis, early implant failure, and nonunion of the fracture. A previous meta-analysis that included 18 studies of patients between 15 and 50 years of age with acute intracapsular hip fractures has reported that these major fracture healing complications occur in approximately 25% of patients.[7] Invariably, these patients endure prolonged morbidity and require further surgery, as confirmed by a 20% re-operation rate in a recent meta-analysis performed by our group.[8] Beyond the prolonged morbidity and increased healthcare costs associated with re-operations, even patients who do not suffer a fracture healing complication frequently experience poor outcomes. This occurs because an additional 30% of femoral neck fractures heal in a shortened or non-anatomic position.[9] This alters the mechanics of the hip, causes the leg to be shorter, and results in substantially worse functional outcomes and quality of life. Therefore, the young femoral neck fracture population is at great risk for experiencing significant fracture healing complications, re-operations, and lifelong morbidity.

1.3 Methods of Internal Fixation

The most common methods of internal fixation for the management of femoral neck fractures are multiple cancellous screws or a single compression screw and sideplate (SHS). Both approaches have strong physiologic rationale; however, there is no clinical consensus regarding the optimal approach for managing femoral neck fractures in young adults. [10]

1.3.1 Multiple Cancellous Screws

Cancellous screws have traditionally been the preferred internal fixation implant for femoral neck fractures.[11] Multiple screws (2 or more) are used during fixation, and advocates of this implant promote the construct's superior torsional stability, limited disruption of femoral head blood supply, minimally invasive insertion, and retention of more viable bone than the SHS.[12,13,14,15,16] Retaining more cancellous bone optimizes vascularity and thus may reduce the risk of femoral head osteonecrosis. In addition, surgeons can insert cancellous screws using small stab incisions with limited blood loss and operating time. This minimally invasive approach may limit damage to the soft tissues around the hip and may plausibly lead to better patient function. The use of cancellous screws has also been supported by two small RCTs. One study compared three cancellous screws versus the larger SHS in patients of all ages and found 3.5-fold greater femoral head vascularity at follow-up bone scanning in patients treated with cancellous screws.[15] The other small RCT compared cancellous screws and SHSs in 30 young adult patients. This study suggested that the use of cancellous screws led to decreased operative time (80% of cases were less than one hour in the cancellous screw group vs. 67% in the SHS group), superior functional outcomes (60% of cases were rated as excellent using the Judet classification system versus 33% in the SHS group), and

fewer complications (2 complications in the cancellous screws group vs. 9 in the SHS group).[17] The small sample size of this study limits our ability to draw definitive conclusions regarding the optimal method of internal fixation.

1.3.2 Sliding Hip Screws

Although cancellous screw fixation has many theoretical benefits and two small RCTs provide evidence supporting its use versus SHS, previous research has suggested that cancellous screws typically fail from bending or shear forces. Since a more vertical high-energy fracture is frequently seen in young adults, proponents of the SHS believe that the implant's biomechanical properties and greater fracture stability are important factors to counteract these forces.[18] Biomechanical studies have shown SHS constructs have 2-fold greater maximal strength and less displacement under physiologic loading conditions compared to cancellous screws.[19] The SHS also performed better than cancellous screws in stabilizing unstable femoral neck fractures using cyclic loading models.[20,14] In addition, two recent retrospective studies comparing cancellous screws and the SHS in young adult fractures have shown substantial reductions in short-term complications using the SHS. Gardner et al[21] showed a 18% absolute risk reduction for re-operation at 6 months (6/29 (21%) patients in the cancellous screw group versus 1/40 (3%) patients in the SHS group). Chen et al[22] reported a 25% absolute risk reduction for reoperation at an average of 15 months (7/28 (25%) patients in the cancellous screw group versus 0/23 (0%) of patients in the SHS group). Other more heterogeneous retrospective studies by Liporace et al[23] and Razik et al[24] suggest Relative Risk Reductions (RRRs) from SHS between 50% to 88% for osteonecrosis of the femoral head and 63% for nonunion. While conclusions from these studies are limited by small sample sizes and the fact that the data are not adjusted for risk, these large reported treatment effects favouring the SHS suggest that a substantial reduction in complications may be achieved by using this alternative surgical implant.

1.3.3 Inconclusive Clinical Evidence

We have conducted two systematic reviews to characterize the outcomes of femoral neck fractures in young patients treated with internal fixation and have performed comprehensive reviews of other relevant literature.[8] These reviews and a meta-analysis by Damany et al[7] document a 25% incidence of fracture complications, a 20% re-operation rate, and a 30% fracture malunion incidence associated with poor quality of life. Our reviews also revealed conflicting data from a small number of studies comparing the SHS and cancellous screws; however, these studies were too heterogeneous to facilitate any quantitative pooling of the results to compare cancellous screw and SHS fixation.

The impact of uncertainty in the surgical literature is further demonstrated by a lack of surgeon consensus. We recently conducted an international survey of orthopaedic surgeons to determine their treatment preferences for the management of young femoral neck fractures.[10] The survey was completed by 540 orthopaedic surgeons. For displaced fractures, 49% of respondents prefer the SHS and 46% prefer cancellous screw

fixation. Despite a near equal split in preference between the SHS and cannulated screws, most surgeons indicated they had treated at least one femoral neck fracture with each device in the past 12 months. The majority of respondents endorsed the need for a RCT comparing SHS and cannulated screws (268/476, 56.3%).

1.4 Adjuvant Nutritional Supplementation (Vitamin D)

Vitamin D is a nutrient that helps the body use calcium and phosphorous to build and maintain strong bones.[25] Vitamin D plays an important role in musculoskeletal health and bone quality because it regulates serum calcium homeostasis. Too little vitamin D can cause calcium and phosphorus levels in the blood to decrease, leading to calcium shifting out of the bones to help maintain stable blood levels.[25]

Laboratory research and human clinical studies suggest important associations between vitamin D, musculoskeletal health, and improved fracture healing. Experimental animal studies have demonstrated the concentration of vitamin D metabolites are higher at a fracture callus compared to the uninjured contralateral bone,[26] vitamin D supplementation leads to decreased time to fracture union and increased callus vascularity,[27] and vitamin D increases mechanical bone strength compared to controls.[28] Clinical studies have also demonstrated that vitamin D supplementation increases the callus volume of proximal humerus fractures,[29] increases the number and diameter of type II muscle fibres,[2] and can improve wound healing.[30] It also has preventative bone health benefits in young adult populations. For example, in a double-blind, placebo-controlled RCT examining the impact of vitamin D on stress fractures in 3,700 navy recruits, a 20% RRR was observed for developing a stress fracture (6.8% experienced a stress fracture in the vitamin D group versus 8.6% in the placebo group).[31] These findings highlight the importance of vitamin D in musculoskeletal health.

By helping to maintain bone health and prevent vitamin D deficiency, the potential benefits of vitamin D supplementation are even more relevant in light of recent research demonstrating that as many as 8 of 10 trauma patients are vitamin D insufficient.[32,33,34] In 201 patients admitted to a level 2 trauma centre for fracture surgery, Bee et al reported the highest prevalence of vitamin D insufficiency was in patients ages 21-40 years (80.5%).[32] Additionally, in a sample of 1,830 fracture patients from a level 1 trauma centre Crist et al reported that 77.4% had vitamin D insufficiency.[33,34] Similar age related results were also found: 79.4% in patients ages 26-35, 81.3% of patients ages 36-45, and 81.6% in patients ages 56-65.[34] The high prevalence of vitamin D insufficiency among young trauma patients combined with the critical microvascular injury at the femoral neck site suggests these fracture patients may face significant barriers to healing and achieving good functional outcomes.

Although the biologic rationale to use vitamin D supplementation to nutritionally optimize the bone of health of young fracture patients is compelling, more clinical research is needed.[35] In this clinical trial, an oral daily dose of 4,000 International Units (IU) of vitamin D_3 has been selected as the route and dose for vitamin D

supplementation. According to a 2010 U.S. Institute of Medicine report jointly commissioned by the U.S. and Canadian governments, 4,000 IU is the Tolerable Upper Intake Level of vitamin D per day for individuals' aged 9 years or older.[36] The rationale for using this dose in the current clinical trial is centred upon our goals of quickly reversing any potential vitamin D insufficiency in a safe and patient-friendly manner. This dose can readily be achieved orally with self-administered pills or drops, and meets the Health Canada criteria for appropriate self-care use.[36] A vast range of other oral dosing regimens have been successfully used in other clinical trials. These include a single administration "megadose" (up to 500,000 IU vitamin D_3 given once), a "megadose" followed by large monthly doses (500,000 IU vitamin D_3 once and monthly 50,000 IU vitamin D_3), and even smaller daily doses alone (1,000 IU vitamin).[37,38] A RCT of hip fracture patients over age 50 demonstrated that there is no advantage of a loading dose in addition to daily supplementation with 1,000 IU vitamin D_3.[38] At 3 months, there was no difference in the serum vitamin D levels between the treatment groups and a similar proportions of patients in each group reached the goal of >75 Nanomole/Litre (nmol/L).[38] Therefore, the daily dose of 4,000 IU of vitamin D_3 should be sufficient to reverse any nutritional insufficiency during the critical first few months of fracture healing.

2. STUDY OBJECTIVES

The objectives of this study are to determine the impact of surgical implants (SHS versus cancellous screw fixation) *AND* nutritional supplementation (vitamin D supplementation versus placebo) on young adults (aged 18-60) with femoral neck fractures. This will be assessed through the following objectives.

2.1 Primary Objective

The primary objective is to assess the impact of surgical implant (SHS versus cancellous screw fixation) *AND* nutritional supplementation (vitamin D versus placebo) on a composite of patient important outcomes during the 12 month post-surgery follow-up period. The composite of patient important outcomes includes: re-operation, femoral head osteonecrosis, severe femoral neck malunion, and nonunion.

2.2 Secondary Objectives

Secondary objectives are to assess the impact of the surgical implants and nutritional supplementation on:

1. Health-related quality of life (HRQL) and functional outcomes
2. Fracture healing complications
3. Radiographic fracture healing

3. TRIAL DESIGN

FAITH-2 is a multi-centre, concealed 2x2 factorial RCT. Surgeons will use one of two surgical strategies in patients who have sustained a femoral neck fracture. The first strategy involves fixation using multiple cancellous screws (cancellous screw group). The second treatment strategy involves fixation of the fracture with a large single diameter

screw and side plate (SHS group). Furthermore, participants will be randomized to receive a nutritional supplement (vitamin D supplementation versus placebo). Our recruitment target is 808 patients with full follow-up. Based on an anticipated conservative 10% loss to follow-up[39], 898 patients will need to be enrolled in the FAITH-2 trial to meet our target sample size. Study personnel at the clinical sites will document critical aspects of peri-operative care and rehabilitation. Clinical assessments will occur at the time of enrollment (baseline), surgery, post-surgery, and 6 weeks, 3 months, 6 months, 9 months, and 12 months post-surgery.

4. METHODS

4.1 Study Setting

The FAITH-2 trial will be conducted at academic and community hospitals across North America, Europe, Australia, Asia, and South America that treat femoral neck fractures in young adults.

4.2 Eligibility Criteria

Wide eligibility criteria will be used to increase the generalizability of the trial.

4.2.1 Inclusion Criteria

1. Adult men or women ages 18 to 60 years.
2. Fracture of the femoral neck.
3. Fracture amenable to both surgical treatments (SHS and cancellous screws).
4. Operative treatment within 7 days of injury.
5. Provision of informed consent by patient or substitute decision maker.

4.2.2 Exclusion Criteria

1. Patients with previously diagnosed osteoporosis.
2. Fracture-dislocation of the femoral neck and hip joint.
3. Planned antegrade nailing of an ipsilateral femoral shaft fracture (if present).
4. Current infection around the hip (i.e. soft tissue or bone).
5. Stress fracture of the femoral neck.
6. Pathologic fractures secondary to neoplasm or other bone lesion.
7. Patients with known or likely undiagnosed disorders of bone metabolism such as Paget's disease, osteomalacia, osteopetrosis, osteogenesis imperfect, etc.
8. Patients with hyperhomocysteinemia.
9. Patient has an allergy to vitamin D or another contraindication to being prescribed vitamin D.
10. Patient is currently taking an over counter drug and/or food supplement that contains vitamin D and is unable or unwilling to discontinue its use for this study.
11. Likely problems, in the judgment of the attending surgeon, with maintaining follow up (e.g. patients with no fixed address, plans to move out of town).

This may include patients with severe mental disorders and drug addictions without adequate support.
12. Pregnancy.
13. Patient is incarcerated.
14. Patient is not expected to survive injuries.
15. The attending surgeon believes the patient should be excluded because they are involved in a conflicting clinical trial.

We will include all femoral neck fracture patterns (subcapital, midcervical, or basicervical). Ipsilateral femoral shaft fractures treated with retrograde nailing or plating will be eligible for inclusion. Patients with multiple traumas will also be eligible for inclusion. Patients with bilateral femoral neck fractures will be eligible for inclusion; however, only the most severe eligible fracture will be included (defined as the most displaced fracture, as determined by the attending surgeon).

4.3 Recruitment Strategy and Patient Screening

All patients presenting to participating surgeons between the ages of 18 to 60 years with a femoral neck fracture will be screened. Potentially eligible patients will be approached to participate in the FAITH-2 trial. All screened patients will be classified as:

1. Excluded (if they subsequently do not meet the eligibility criteria).
2. Missed (eligible but not randomized due to error).
3. Included (eligible and randomized).

4.4 Randomization Methods

Eligible patients will be randomized in equal proportions to one of four treatment groups: 1) cancellous screws with vitamin D_3 supplementation, 2) cancellous screws with placebo supplementation, 3) SHS with vitamin D_3 supplementation, or 4) SHS with placebo supplementation. Allocation will be concealed using a centralized 24-hour computerized randomization system that will allow Internet based allocation. The treatment allocation will be stratified on the following prognostic factors to ensure balance between the intervention groups: 1) undisplaced or displaced femoral neck fractures; 2) presence or absence of an ipsilateral femoral shaft fracture; and 3) geographic region of recruiting centre (industrializing countries versus industrialized countries).

4.5 Surgical Interventions

4.5.1 Multiple Cancellous Screws

Participants allocated to the cancellous screw group will receive multiple threaded screws (with a minimum of 3 screws and a minimum diameter of 6.5 mm) (**Figure 2**). Any threaded screw or hook pin as well as buttress plates will be permitted. The number of screws, screw configuration, reduction technique, implant manufacturer, use of buttress plates, decision to perform a capsulotomy, use of injectable bone substitutes,

use of bone grafts, or aspiration of an intracapsular hematoma will be documented but not prescribed due to lack of evidence favouring any of these approaches.

4.5.2 Sliding Hip Screws

Participants allocated to the SHS group will receive a single larger diameter partially threaded screw affixed to the proximal femur with a sideplate using a minimum of 2 screws for fixation (**Figure 3**). Surgeons will be permitted to use any fixed-angle plate construct which includes a large diameter screw or blade that can slide within the plate. Surgeons will be allowed to use derotational screws and buttress plates. The use of a compression screw, implant manufacturer, reduction technique, decision to perform a capsulotomy, use of injectable bone substitutes, use of bone grafts, and aspiration of intracapsular hematoma will be documented but not prescribed.

4.5.3 Ipsilateral Femoral Shaft Fractures

Ipsilateral femoral shaft fractures will be treated with plating or retrograde nailing. The method of fixation will be documented. We will also document the following outcomes on the shaft fracture: 1) the time to radiographic fracture healing of the ipsilateral femoral shaft; 2) re-operation; and 3) fracture-related complications.

4.5.4 Adherence to Surgical Intervention

Crossovers rates between the SHS and multiple cancellous screw groups are likely to be low because both implants are inserted with similar techniques and surgeon expertise in both techniques is likely to be very similar. Participants will be randomized as close to surgery as possible. Any participants who crossover will be analyzed in the group to which they were allocated, maintaining the intention to treat approach for the analysis.

4.6 Nutritional Supplementation

4.6.1 Administration of Nutritional Supplementation

Nutritional supplementation will be administered upon hospital discharge or within two weeks of the participant's femoral neck surgery, whichever comes first. Ideally, participants should be administered the nutritional supplementation as soon as possible following their surgery. Each participant will be provided with a six-month supply of vitamin D_3 supplementation or placebo.

4.6.2 Vitamin D Supplementation

Participants allocated to the vitamin D Group will receive a bottle of 2,000 IU vitamin D_3 drops (Ddrops®, Ddrops Company). Participants will be instructed to take two drops daily for six months, for a total daily dose of 4,000 IU. All vitamin D_3 supplement bottles will be labeled in a blinded manner according to Health Canada guidelines and Good Manufacturing Practice.

4.6.3 Placebo Supplementation

Participants in the placebo group will receive an identical bottle of placebo drops with no active ingredient. Similarly, they will be instructed to take two drops daily for six months. The placebo supplement is also manufactured by the Ddrops Company. All placebo supplement bottles will be labeled in a blinded manner according to Health Canada guidelines and Good Manufacturing Practice.

4.6.4 Adherence to Nutritional Supplementation

Crossovers are unlikely between the nutritional supplementation groups as participants and surgeons will be blinded to the vitamin D and placebo treatments. Additionally, participants will be explained the importance of treatment compliance at each follow-up visit. Study personnel will be instructed that prescribing study participants vitamin D is prohibited. Participants will also be instructed to not take additional supplements containing vitamin D for the duration of the trial. Previous research has demonstrated a 96% adherence to daily vitamin D self-administration in adults[40]. Additionally, the nutritional treatment arm represents a pragmatic effectiveness comparison, and given the placebo-controlled blinding, there is no reason to suspect differential compliance between the treatment groups will occur. We will document any deviations to the adherence to nutritional supplementation.

4.7 Standardization of Peri-Operative Care

To ensure similar peri-operative regimens participants should receive antibiotic prophylaxis (i.e. cephalosporin, or equivalent coverage) within one hour prior to surgery. Weight bearing status will be determined by the participants' attending surgeon and we will document the participants' weight bearing status at each visit. We will also document surgical delay and whether the participant received physiotherapy.

4.8 Primary and Secondary Outcome Measures

4.8.1 Primary Outcome

The primary outcome will be a composite of patient important outcomes that occur within the 12 months post-surgery follow-up period. Specifically, these are limited to:

1. *Re-operation:* any unplanned surgery related to the treatment of the femoral neck fracture;
2. *Femoral head osteonecrosis:* any evidence of osteonecrosis on any follow-up medical imaging study (i.e., radiographs, magnetic resonance imaging (MRI), or other advanced imaging study);
3. *Severe femoral neck malunion:* fracture healing with femoral neck shortening of >10 mm in any plane on follow-up x-rays;[9] or
4. *Nonunion:* failure of the fracture to progress towards healing defined as a Radiographic Union Score for Hip (RUSH)[41,42] score below a pre-determined threshold specific for nonunion at 6 months or greater post-injury.

4.8.2 Secondary Outcome

The secondary outcomes will include:

1. HRQL and patient-reported function as measured by the:
   - Short Form-12 (SF-12)[43] which measures self-reported quality of life through an 8-domain profile of functional health and well-being, physical and mental health summary measures and a preference-based health utility index.
   - Hip Outcome Score (HOS)[44] which measures self-reported functional status through 28 items and two sub-scales that pertain to activities of daily living (ADLs) or higher level activities such as those necessary to participate in sports.
2. Fracture healing complications: These will include wound healing problems, infection (superficial and deep), hardware failure, hardware breakage, painful hardware, and peri-prosthetic fracture.
3. Radiographic fracture healing: The date of healing will be determined by the Central Adjudication Committee (CAC). They will consider a fracture as healed when there is obliteration of the fracture line by newly formed bone along the cortices and within the trabecular bone on anterior-posterior and lateral radiographs.

4.9 Frequency and Duration of Follow-Up

Participants will be followed for a period of 12 months post-surgery (**Figure 4**). Participant follow-up visits will occur at enrollment (baseline), post-operative (24 hours to 14 days window), 6 weeks (2 week to 8 week window), 3 months (2 to 4 month window), 6 months (5 to 7 month window), 9 months (7 to 11 month window), and 12 months (11 months or greater window) post-surgery.

The **Schedule of Assessments** (**Table 1**) details the requirements and procedures for each visit. All study outcomes (as defined in sections 4.8.1 and 4.8.2) will be documented on the case report forms (CRFs) at each follow-up visit.

Additionally at all follow-up visits the participant will complete the SF-12 and HOS questionnaires. At the post-surgery follow-up visit participants will answer all questionnaires based on their pre-injury status. Questionnaires for subsequent follow-up visits will be answered based on the participant's current status at the time of follow-up.

For participants who have an ipsilateral femoral shaft fracture at each follow-up visit we will document: 1) the time to radiographic fracture healing of the ipsilateral femoral shaft; 2) re-operation; and 3) fracture-related complications including compartment syndrome, wound healing problems, infection (superficial or deep), hardware failure, hardware breakage, malunion, nonunion, and prolonged pain at the fracture site.

Serious adverse events (SAEs) will also be documented at each visit. X-rays of the participant's fractured hip are required at enrollment (baseline), post-surgery, and at, 6

weeks, 3 months, 6 months, 9 months, and 12 months post-surgery. As the primary outcome includes radiographic outcomes, it is important that X-rays be obtained at all follow-up visits. MRI or other advanced imaging studies are not required and may be ordered at the discretion of the attending surgeon. Clinical notes may also be requested. If additional imaging studies are obtained, they will be sent to the Methods Centre for outcome adjudication. In addition, at the 12-month follow-up visit, any re-operations that may be planned for the participant will be documented.

4.10 Participant Retention

Once a patient is enrolled in the trial, the clinical site will make every reasonable effort to follow the participant for the entire duration of the study period. The expected follow-up rate for this study is greater than 90% based on similar fracture trials performed by the study investigators.[39,45] To maximize participant retention, all possible attempts should be made to collect as much data as possible and to reduce loss to follow-up. We have implemented procedures to improve participant retention (**Figure 5)**.[46] Clinical site personnel are responsible for implementing these procedures, as well as developing their own local procedures, in order to attain this follow-up rate.

Participants may discontinue their participation in the FAITH-2 study at any time. If a participant wishes to withdraw their consent from the study, we will use the following strategies to reduce the demands of the study and help to retain the study participant:

1. Ask them to return for a clinic visit at the 12 month follow-up only and ensure that the items included in the primary outcome (re-operation status and X-ray) are completed.
2. Ask them if research personnel may contact them by telephone to ask about their status.
3. Ask them for permission to access their medical chart to identify information about their status.

We will only deem participants lost to follow-up after all exhaustive measures have been taken to locate the participant. Participants should not be deemed lost to follow-up until the 12 month visit is due and all attempts to contact the participant have been exhausted.

We will not remove participants from the study if the study protocol was not adhered to (e.g. participant received wrong treatment arm, early discontinuation of nutritional supplement, occurrence of protocol deviations, missed follow-up visits, etc.). We will document the reasons for participant withdrawal from the trial (e.g. withdrawal of consent or lost to follow-up).

4.11 Blinding

Surgeons, research personnel, participants, and members of the CAC cannot be blinded to the treatment allocation of the surgical interventions (SHS versus cancellous screws).

The data analyst and the Steering Committee will be blinded to the surgical treatment allocation.

The complete blinding of the nutritional supplement will be achieved by using vitamin D_3 and placebo liquid products that are indistinguishable. This will ensure that the surgeon, participants, research personnel, the CAC members, the data analyst, and the Steering Committee are blinded to the participants' nutritional supplementation allocation. An unblinding procedure will be made available when necessary (**Figure 6**).

5.0 STATISTICAL PLAN

5.1 Sample Size Determination

The choice of sample size is based upon independent comparisons of the SHS versus multiple cancellous screw *AND* vitamin D supplementation versus placebo for the primary outcome (patient important outcomes). This is based on the assumption that both interventions will act independently. We will use an alpha level of 0.5 for the primary outcome and all statistical hypotheses will be 2-sided.

The preliminary sample size calculations are based on the limited published literature. As outlined in section 1.2, a pooled estimate from 18 published studies revealed a combined femoral head osteonecrosis and fracture nonunion incidence of 25%. In addition to femoral head osteonecrosis, the composite primary outcome includes other events such as re-operation and severe femoral neck malunion. These additional complications are expected to increase the composite event rate to approximately 40%; therefore, a conservative event rate of 30% is assumed in the cancellous screw and placebo groups.

The trial is powered for a RRR of 33% for each of the treatment comparisons: SHS versus multiple cancellous screws *AND* vitamin D_3 supplementation versus placebo. This RRR estimate is based on the best available literature and coincides with a 10% absolute risk reduction that was deemed to be clinically significant by over 500 surveyed surgeons. [10] For the surgical comparison, Gardner et al[21] and Chen et al[22] reported an 86% and 100% RRR for reoperation using a SHS. Other more heterogeneous retrospective studies by Liporace et al[23] and Razik et al[24] suggest RRRs from SHS between 50-88% for osteonecrosis and 63% for nonunion (Section 1.3). Since these are uncontrolled retrospective studies, a conservative effect size estimate is maintained. With regard to the expected treatment effect of vitamin D supplementation, there are no clinical studies that quantify its efficacy to reduce fracture healing complications. Despite the lack of direct data, vitamin D supplementation following acute fractures has demonstrated a 40% increase in fracture callus density in human participants[29] and an 80% increase in mechanical strength in animal model.[28] Experimental evidence also suggests benefits of increased fracture area vascularity and improved healing that may also contribute to the treatment effect of vitamin D supplementation. We have also assumed the same RRR of 33% in the vitamin D treatment arm.

Considering a 30% event rate in the cancellous screw and placebo group, a RRR of 33% will give a 20% event rate in the SHS and placebo group. Therefore, the event rate for the total placebo group (combined over cancellous screw and SHS groups) is expected to be 25%. Similarly a RRR of 33% due to vitamin D_3 supplementation will result in a 20% event rate in the cancellous screw and vitamin D_3 supplementation group. This leads to an expected event rate of 25% for the total cancellous screw group (combined over both the placebo and vitamin D_3 supplementation groups). Therefore our sample size calculation is based on a control group event rate of 25% and a RRR of 33%.

We will recruit a sample size of 808 patients with full follow-up. Based on an anticipated 10% loss to follow-up[39], 898 patients will need to be enrolled in the FAITH-2 trial. **Table 2** demonstrates that the chosen sample size will have a high likelihood of detecting a RRR of 33% or greater across a plausible range of expected primary outcome events (patient important complication), and moderate power for slightly lower effect sizes. Furthermore, if there are synergistic effects between the surgical and vitamin D interventions, there will be even greater study power.

5.2 Statistical Methods

5.2.1 General

The baseline characteristics will be analyzed using descriptive statistics reported as mean (standard deviation) or median (first quartile, third quartile) for continuous variables depending on the distribution and count (percent) for categorical variables. All outcome analyses will adhere to the intention-to-treat principle. The reporting of the trial will follow the CONSORT criteria (www.consort-statement.org). We will provide estimates of our composite outcome of patient important outcomes using proportions with 95% confidence intervals and associated p-values. All p-values will be reported to three decimal places with those less than 0.001 reported as $p<0.001$. The criterion for statistical significance will be based on alpha = 0.05. We will use SAS (Cary, NC) to perform all analyses.

5.2.2 Primary Analyses

Two independent comparisons between the treatment groups (SHS versus cancellous screws *AND* vitamin D_3 supplementation versus placebo) will be made using the chi-square statistic and an alpha level of 0.05. **Table 3** shows the details for the analysis of primary outcomes.

5.2.3 Secondary Analyses

All secondary outcomes will be summarized using means and 95% confidence intervals, or percentages and 95% confidence intervals. Longitudinal models will be used to explore the effect of treatment group and time on the HOS and SF-12 patient-reported outcomes. **Table 4** shows the details for the analysis of secondary outcomes.

5.2.4 Planned Exploratory Analyses

Exploratory analyses will be conducted comparing the treatment effects in participants with undisplaced versus displaced femoral neck fractures, and emergent (<8 hours) versus non-emergent (≥8 hours) internal fixation. We plan to fit logistic regression models and include treatment by subgroup interactions to assess whether the magnitude of the treatment effect is significantly different between subgroups. **Table 5** shows the details for the exploratory analyses.

5.2.5 Interim Analysis

An interim analysis will not be conducted. The trial will not be stopped early for benefit. The Data Safety and Monitoring Committee (DSMC) will monitor Adverse Events (AEs) and may make recommendations to the Principal Investigators and Steering Committee to stop the study for harm only.

6. DATA MANAGEMENT

6.1 Case Report Forms and Data Entry

The CRFs will be the primary data collection tool for the study. All data requested on the CRF must be recorded. An Electronic Data Capture (EDC) system will be used to submit data to the Methods Centre located at McMaster University. Upon receipt of the data, the personnel at the Methods Centre will make a visual check of the data and they will query all missing data, implausible data, and inconsistencies.

6.2 Data Transmissions

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

6.3 Data Discrepancy Inquiries

Once data are submitted, additional errors will be detected by the program within the EDC system to detect missing data or errors. Clinical site personnel will be notified of these errors through regular quality control reports. Clinical site personnel will be required to respond promptly to each query on the quality control report. To respond to queries study personnel should check the original forms for inconsistency and check other sources of participant records to determine the correction. Clinical site personnel will then modify the data in the EDC system to reflect the correction and resubmit data to the Methods Centre in order to resolve the query.

6.4 Security and Back-Up of Data

All CRFs and specimens must be kept secure in locked cabinets or other enclosures that are accessible only to study personnel. All electronic data must be password-protected and accessible only to study personnel. The Methods Centre will be responsible for backing up all submitted data.

6.5 Quality Control Reports

Each clinical site will regularly receive a quality control report showing the number of each of the following:

1. Participants entered into the trial.
2. Completed follow-ups.
3. Outstanding data queries and clarification requests.
4. Participant's next follow-up visit.
5. Overdue follow-up visits.

Study personnel should review these reports for accuracy and contact the Methods Centre if they identify any discrepancies.

7. ETHICS AND DISSEMINATION

7.1 Research Ethics Approval

This protocol, the consent form template, and the CRFs will be reviewed and approved by McMaster University's Research Ethics Board (REB). The protocol, clinical site-specific informed consent forms, and any participant recruitment material will need to be reviewed and approved by each clinical site's local ethics board. Prior to commencement of the study the clinical site must provide the Methods Centre with a copy of the ethics board approval.

7.2 Consent

Any patients who are deemed to meet all eligibility criteria should be approached to discuss participation in the trial by someone on the study team who is knowledgeable about the trial. In order to obtain informed consent, study personnel should follow the below procedures:

- Present study information in a manner that is understandable to the potential participant/the patient's legal representative.
- Discuss the study with the potential participant/the patient's legal representative and answer any questions he or she asks.
- Allow the potential participant/the patient's legal representative an opportunity to discuss participation with their family, friends, or family physician if desired.
- Confirm that the participant/the patient's legal representative understands the risks and benefits of participating in the study and that their participation is voluntary.
- Complete and obtain signatures for informed consent form and obtain contact information from the participant.

7.3 Confidentiality

Information about study participants will be kept confidential and will be managed in accordance with the below rules:

- All study-related information will be stored securely at the clinical site.
- All study participant information will be stored in locked file cabinets and accessible only to study personnel.
- All CRFs will be identified only by a coded participant number and initials.
- All records that contain participant names, or other identifying information (e.g. consent forms and contact information forms), will be stored separately from the study records that are identified only by the coded participant number and initials.
- All local databases will be password protected.

In the event that a participant revokes authorization to collect or use personal health information (PHI), the clinical site retains the ability to use all information collected prior to the revocation of participant authorization. For participants that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. primary outcome data) at the end of their scheduled study period.

7.4 Access to Data

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. All requests will be reviewed by the Principal Investigators.

7.5 Protocol Amendments

Any amendments to the study protocol which may affect the conduct of the study, or the potential safety of or benefits to participants (e.g. changes to the study objectives, study design, sample size, or study procedures) will require a formal amendment to the protocol. Any protocol amendments will be approved by the Principal Investigators and will require approval by McMaster University's REB. Clinical sites will also be required to submit amendment requests to their local ethics boards in order to obtain approval for the amendment and to provide the Methods Centre with a copy of this approval. Administrative changes (e.g. minor corrections or clarifications that have no effect on the way the study is conducted) will not need to undergo a formal amendment process and will be communicated to clinical sites when applicable.

7.6 Adverse Event Reporting and Definitions

7.6.1 Adverse Event

An AE is any symptom, sign, illness, or experience that develops or worsens in severity during the course of this study. As FAITH-2 is not assessing patient safety, only AEs that are study outcomes (i.e. fracture-related) will be recorded as per sections 4.8.1 and 4.8.2.

7.6.2 Serious Adverse Event

AEs are classified as serious or non-serious. A SAE is any AE that is any of the following:

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

All SAEs must be recorded and promptly submitted to the Methods Centre.

7.6.3 Unanticipated Problems Resulting in Risk to Participant or Others

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

- Unexpected in nature, severity, or frequency (e.g. not described in study-related documents such as the ethics-approved protocol or consent form, etc.).
- Related or possibility related to participation in the research (i.e. possibly related means there is reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research).
- Suggests that the research places participants or others at greater risk of harm (including physical, psychological, economic, or social harm).

All unanticipated problems resulting in risk to participants or others must be recorded and promptly submitted to the Methods Centre.

7.7 Reporting of Serious Adverse Events and Unanticipated Problems Resulting in Risk to Participants or Others

All fracture-related AEs, SAEs, and unanticipated problems resulting in risk to participants or others are to be reported to the Methods Centre immediately.

7.7.1 Clinical Site Reporting: Notifying the Methods Centre

All fracture-related AEs and SAEs must be reported to the Methods Centre by completing the AE form and submitting it to the Methods Centre. The clinical site will keep a copy of this form on file at the clinical site. Significant new information on ongoing SAEs should be provided promptly to the Methods Centre by updating the form. Unanticipated problems resulting in risk to participants or others are to be reported to the Methods Centre.

7.7.2 Clinical Site – Institutional Review Board and Research Ethics Board Reporting

Clinical sites are responsible for reporting fracture-related AEs, SAEs and unanticipated problems resulting in risk to participants or others to their local ethic boards. Clinical sites are responsible for complying with their local ethic boards reporting requirements. Copies of each report and documentation of ethic board notification and receipt will be kept in the clinical site's study file.

7.8 Potential Risks to Participants

Surgeons worldwide are currently using both surgical techniques (cancellous screws and SHS). Both implants have been used for over five decades in the management of hip fractures. As with any surgical procedure of the lower extremity, potential risks include wound infection, deep vein thrombosis, neurovascular injury, and death. Given that all eligible patients require surgery for their acute fracture, there is no anticipated increased surgical risk for study participants. Similarly, the safety of vitamin D_3 supplementation is well established, and 4,000 IU per day is within the tolerable daily dose according to Health Canada.[36] Participants will be monitored for all SAEs and fracture-related AEs following treatment across the surgical and nutritional arms. The DSMC will review SAEs and fracture-related AEs at regular intervals.

7.9 Dissemination Policy

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.

7.10 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice and International Conference on Harmonization guidelines, applicable government regulations, and institutional research policies and procedures.

8. STUDY COMMITTEES

8.1 Steering Committee

The Steering Committee is comprised of orthopaedic surgeons, vitamin D experts, a statistician, and research methodologists. The Steering Committee will provide guidance and direction to the overall trial.

8.2 Data Safety and Monitoring Committee

The DSMC is comprised of 3 members who remain completely independent of the study investigators. The DSMC members include a biostatistician (Chair) and two orthopaedic surgeons with prior trial experience. The DSMC will review accumulated safety data (i.e. SAEs and fracture-related AEs) from the trial and advise the Principal Investigators and the Steering Committee on items related to participant safety.

8.3 Central Adjudication Committee

The CAC will be comprised of four orthopaedic surgeons with prior adjudication experience and they will independently adjudicate the following:

- Situations where eligibility is in doubt
- Radiographic characteristics and quality of the surgery
- Patient important outcomes that define the primary outcome (re-operation, femoral head osteonecrosis, severe femoral neck malunion, or nonunion)
- Fracture healing complications
- Radiographic fracture healing

All clinical sites will submit X-Rays and any additional imaging studies (such as a hip MRI or other advanced imaging studies) to be included in the adjudication process (**Figure 7**). Clinical notes may also be requested. Any disagreements between the CAC members will be resolved during regular conference calls. If consensus cannot initially be reached, additional information will be requested from the clinical site to clarify areas of uncertainty.

Table 1: Schedule of Events

Assessment	Screening	Enrollment (Baseline)	Surgery	Post-operative	Week 6	Month 3	Month 6	Month 9	Month 12
Informed Consent	X								
Medical History	X								
AP & Lateral X-Rays of Proximal Femur	X			X	X	X	X	X	X
Physical Exam/Injury Assessment	X								
Screening Form	X								
Randomization Form		X							
Pre-Operative Form		X							
Surgery (SHS or Cancellous Screws)			X						
Surgical Forms			X						
Hospital Discharge Form				X					
Vitamin D or Placebo Supplementation**				X	X	X	X		
Follow-up Visit Forms				X	X	X	X	X	X
Assessment for Re-Operations				X	X	X	X	X	X
Assessment of Fracture Healing Complications					X	X	X	X	X
Assessment of Fracture Healing					X	X	X	X	X
Hip Outcome Score (HOS)				X*	X	X	X	X	X
Short Form-12 (SF-12)				X*	X	X	X	X	X
Assessment of Fracture Healing of the Ipsilateral Femoral Shaft Fracture***					X	X	X	X	X
Assessment for Fracture-Related Adverse Events			X	X	X	X	X	X	X
Assessment for Serious Adverse Events			X	X	X	X	X	X	X
Assessment for Planned Re-operations									X

*Asks about participant's function prior to their hip fracture.

** Nutritional supplementation will be administered upon hospital discharge or within two weeks of the participant's surgery, whichever comes first. Ideally, participants should be administered the nutritional supplementation as soon as possible following their surgery to repair their femoral neck fracture.

***For participant's with an ipsilateral femoral shaft fracture.

Table 2: Sample Size Estimates

		Relative Risk Reduction from the SHS and vitamin D supplementation					
		20%	**25%**	**30%**	**33%**	**35%**	**40%**
Incidence of Patient Important Outcomes in the control groups	**20%**	2994	1890	1294	1060	936	706
	25%	2266	1434	984	**808**	714	540
	30%	1782	1130	778	638	566	428
	35%	1436	914	630	518	460	348
	40%	1178	752	520	428	380	288

- Total sample size required to achieve 80% power for the independent comparisons of the SHS versus cancellous screws AND vitamin D supplementation versus placebo.
- Grey highlighted boxes denote scenarios where we have more than 80% power (alpha=0.05, 2-sided) to detect the hypothesized difference, given our proposed sample size of 808.
- Control groups: cancellous screws and placebo supplementation

Table 3: Summary of Primary Outcome Analyses

Variable/Outcome	Hypothesis for Surgical Treatments	Hypothesis for Nutritional Supplementation	Outcome Measures	Method of Analysis
Re-operation	The incidence of re-operation, femoral head osteonecrosis, severe femoral neck malunion, or nonunion will be lower in patients receiving a SHS compared to cancellous screws.	The incidence of re-operation, femoral head osteonecrosis, severe femoral neck malunion, or nonunion will be lower in patients receiving vitamin D versus placebo.	Re-operation anytime within 12 months	*Chi-square statistic* with independent comparison for the surgical treatments and nutritional treatments (alpha=0.05)
Femoral head osteonecrosis			Evidence of femoral head osteonecrosis on X-Rays or MRI	
Severe malunion			Evidence of severe femoral neck malunion on X-Rays	
Nonunion			Failure of the fracture to progress towards healing defined as a Radiographic Union Score for Hip (RUSH)[41,42] score below a pre-determined threshold specific for nonunion at 6 months or greater post-injury	

*The primary outcome is a composite of re-operation, femoral head osteonecrosis, severe femoral neck malunion, or nonunion.

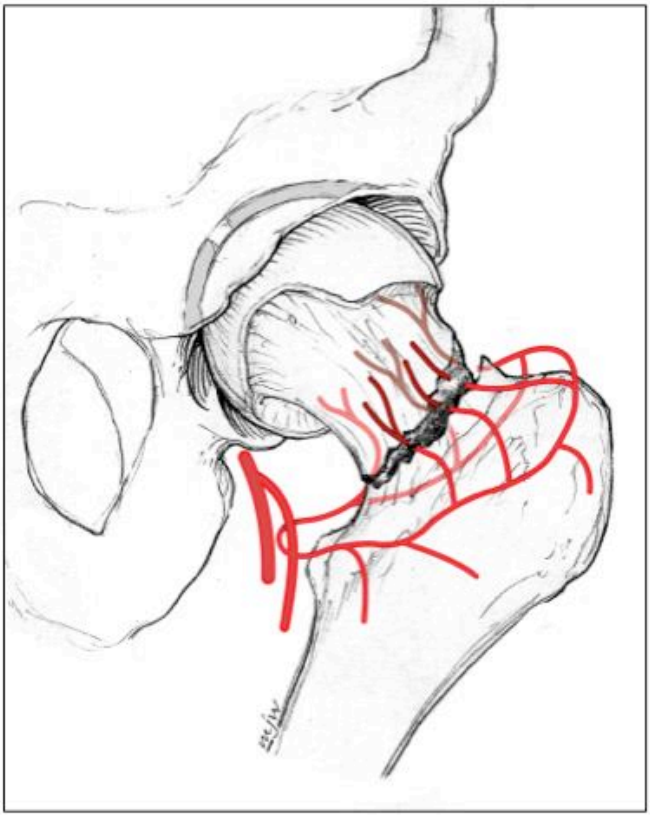
Table 4: Summary of Secondary Analyses

Variable/Outcome	Hypothesis for Surgical Treatments	Hypothesis for Nutritional Supplementation	Outcome Measures	Method of Analysis
HRQL and function	HRQL and function will be better in patients receiving SHS versus cancellous screws.	HRQL and function will be better in patients receiving vitamin D versus placebo.	HOS and SF-12	Summary statistics of means and confidence interval Longitudinal modeling to include treatment and time
Fracture healing complications	Rates of fracture healing complications will be lower in patients receiving SHS versus cancellous screws.	Rates of fracture healing complications will be lower in patients receiving vitamin D versus placebo.	Evidence of complications reported by patients or evident on X-Rays	Summary statistics of proportions *Chi-square statistic* with independent comparison for the surgical treatments and nutritional treatments
Fracture healing	Fractures will heal faster in patients receiving SHS versus cancellous screws.	Fractures will heal faster in patients receiving vitamin D supplementation.	A fracture will be considered as healed when there is obliteration of the fracture line by newly formed bone along the cortices and within the trabecular bone on anterior-posterior and lateral X-rays	Time to event analysis with treatment group as an independent variable

Table 5: Summary of Exploratory Analyses

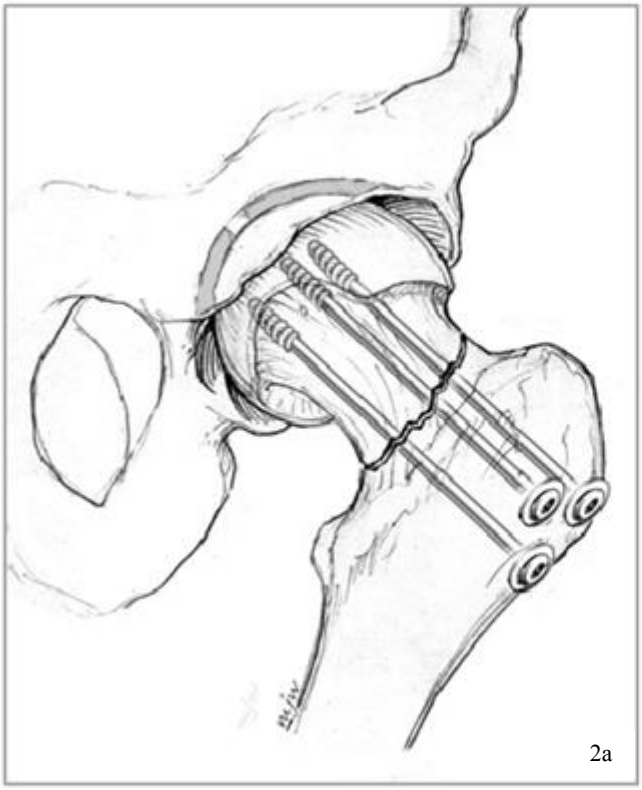
Fracture/Surgical Characteristics	Hypothesis for Surgical Treatments	Hypothesis for Nutritional Supplementation	Outcome Measures	Method of Analysis
Undisplaced versus displaced femoral neck fractures	The magnitude of treatment effect favouring SHS will be higher in displaced fractures vs. undisplaced fractures	The magnitude of treatment effect favouring vitamin D will be higher in displaced fractures vs. undisplaced fractures	Composite primary outcome as above (reoperation, femoral head osteonecrosis, severe femoral neck malunion, and nonunion)	Logistic regression models with an interaction term between treatment and femoral neck displacement
Emergent (<8 hours) versus non-emergent (≥8 hours) internal fixation	The magnitude of treatment effect favouring SHS will be higher in fractures treated emergently vs. non-emergently.	Not Applicable	Composite primary outcome as above (reoperation, femoral head osteonecrosis, severe femoral neck malunion, and nonunion)	Logistic regression models with an interaction term between treatment and internal fixation type

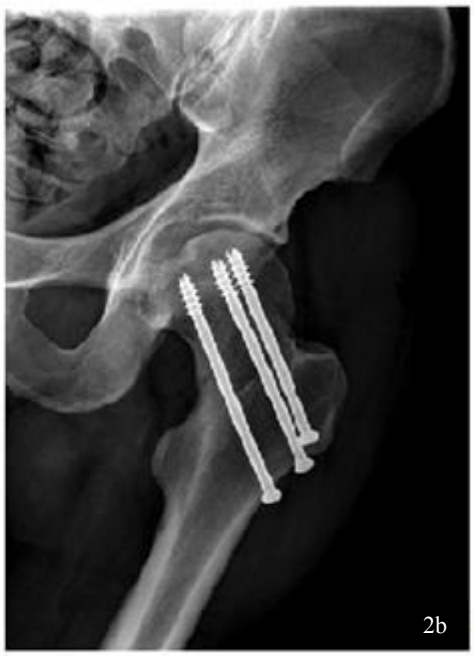
Figure 1: Blood Supply to the Femoral Head



The femoral head and neck are perfused by a ring of small blood vessels. These fragile capsular vessels are most vulnerable to injury at the femoral neck and are frequently torn during the fracture. Disrupting the local blood supply leads to femoral head osteonecrosis (bone death) and femoral neck nonunion (the fracture does not heal)

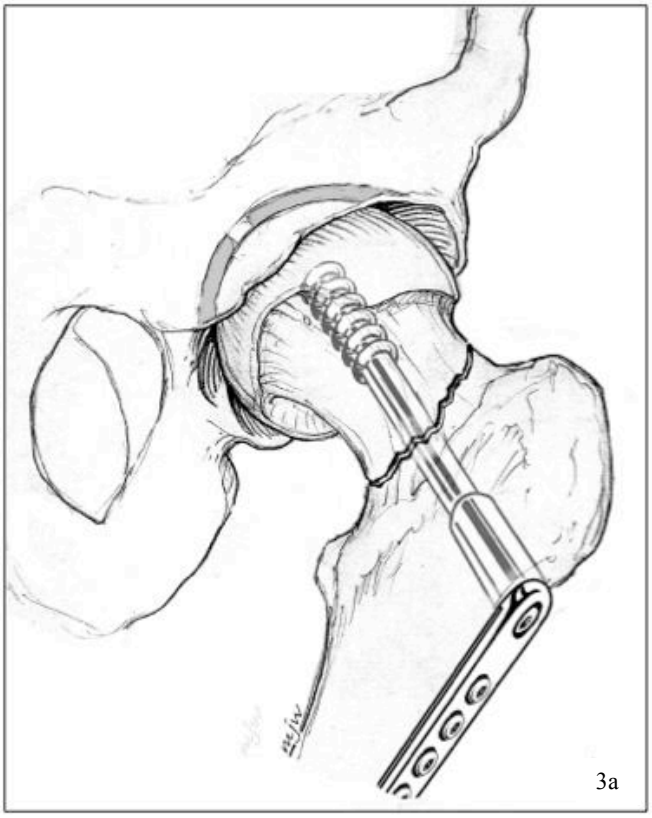
Figure 2: Multiple Cancellous Screws

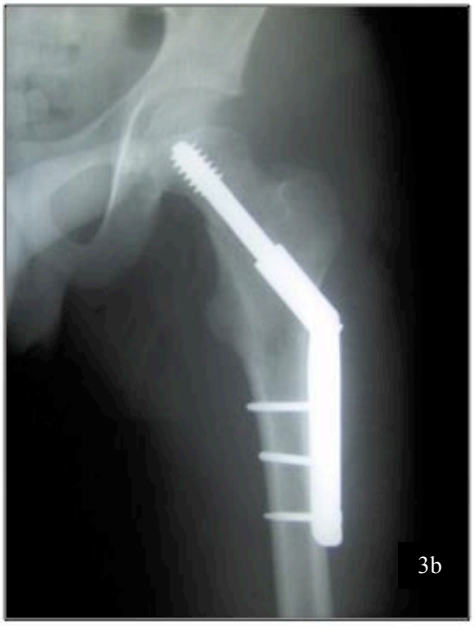




2a Diagram of screw fixation
2b X-ray depiction of screw fixation

Figure 3: Sliding Hip Screw





3a Diagram of sliding hip screw
3b X-ray depiction of sliding hip screw

Figure 4: Recruitment and Follow-Up Schedule

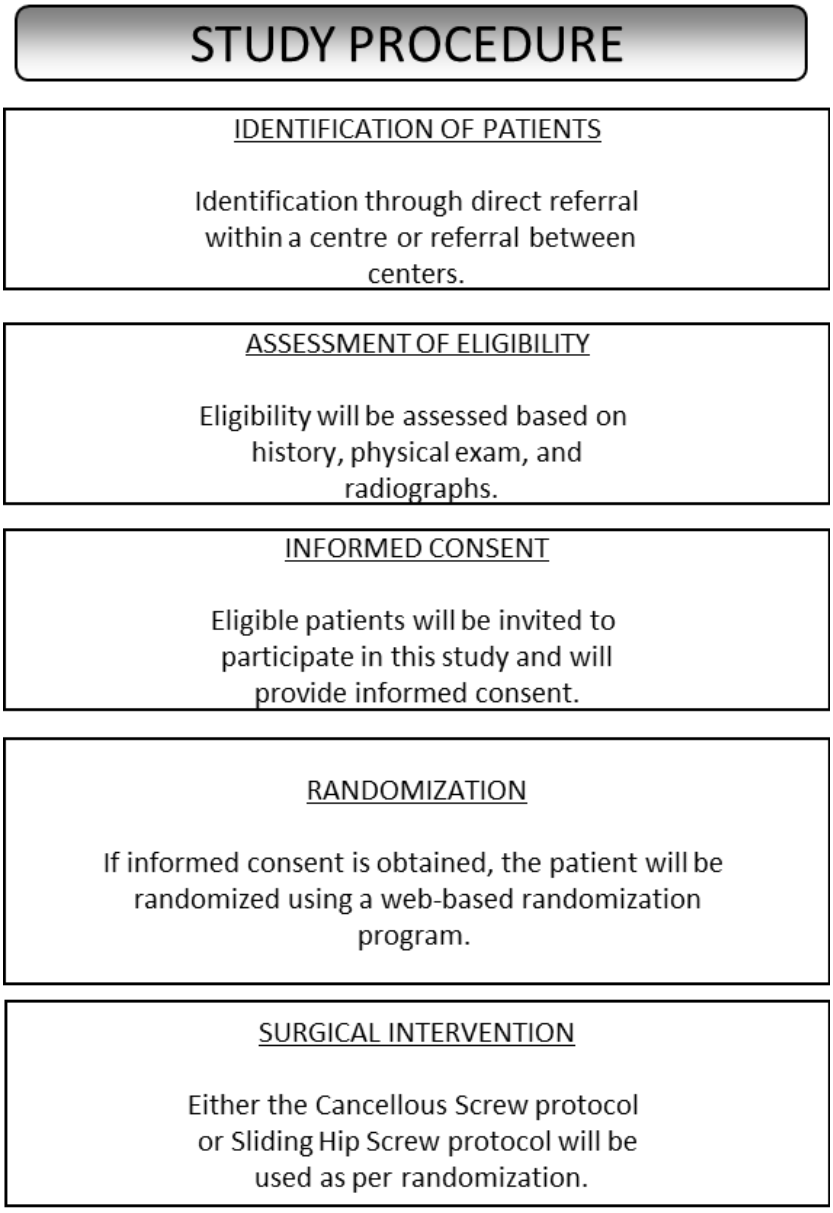


Figure 4: Recruitment and Visit Schedule (continued)

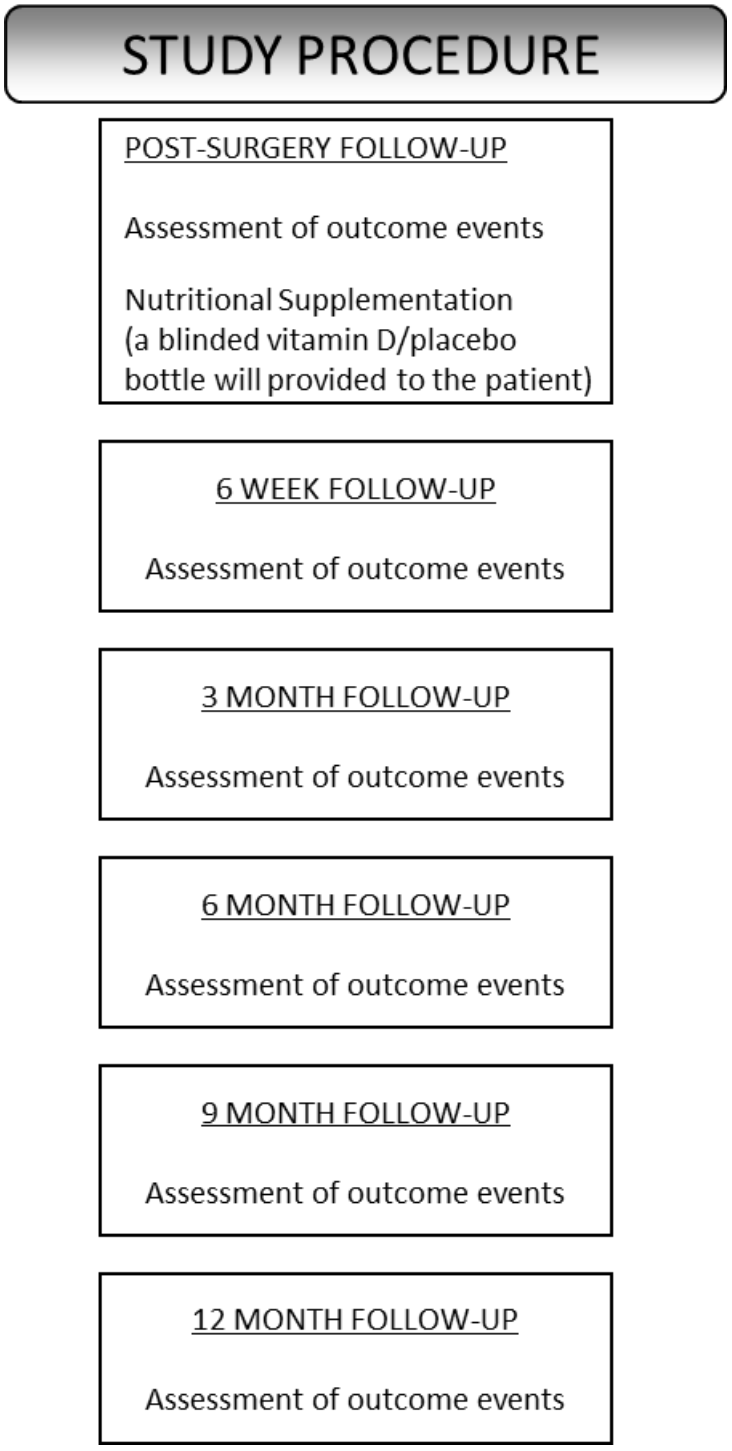


Figure 5: Retention Strategies

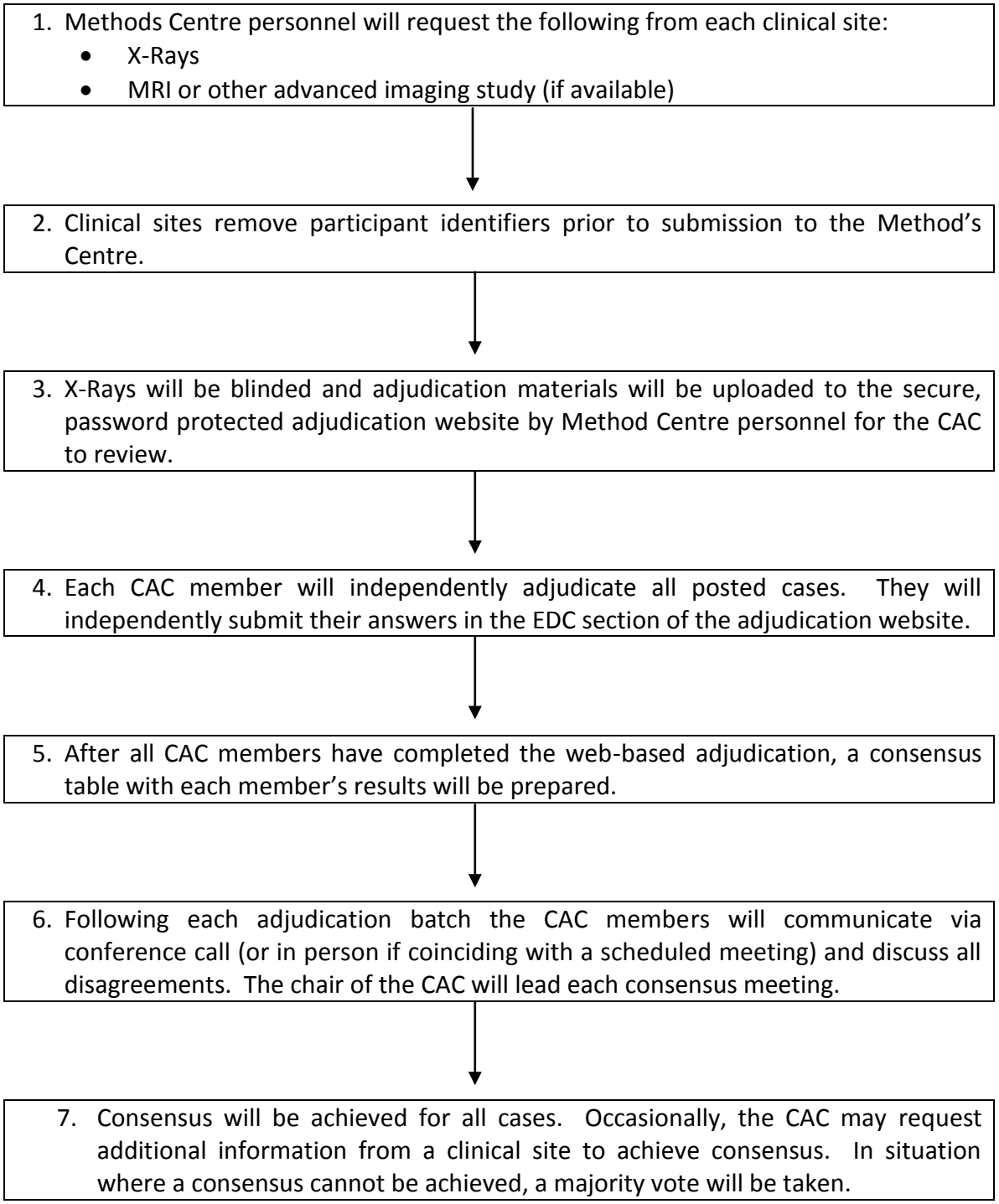
1) We will exclude individuals who are likely to present problems with follow-up (see exclusion criteria).
2) At the time of randomization, as well as their own address and phone number, each participant will provide the name and address of their primary care physician, and the name, address and phone number of three people at different addresses with whom the participants does not live who are likely to be aware of the participant's whereabouts. The research coordinator will confirm that these numbers are accurate prior to the participant's discharge from hospital.
3) Participants will receive reminders for upcoming clinic visits from local study personnel.
4) Follow-up schedules will coincide with normal surgical fracture clinic visits.
5) Study personnel will contact participants no less frequently than once every three months to maintain contact and obtain information about any planned change in residence.
6) If a participant refuses to return for a follow-up assessment, study personnel will reduce the burden of the study assessments and aim to have the participant complete the primary outcome only.

Sprague et al[46]

Figure 6: Unblinding of Clinical Site Personnel for Emergency Medical Management

1. In the event of a medical emergency that directly affects the health status of the participant, it may become necessary to unblind allocation status to determine the specific treatment the participant has received while enrolled in the study. A medical emergency is defined as an event which necessitates immediate attention regarding the treatment of a participant.
2. Clinical sites are instructed to contact the Methods Centre and provide details of the medical emergency as soon as possible after the event. At no time will the participant's health be compromised or medical treatment delayed.
3. When a request for unblinding is received by the Methods Centre, the Research Coordinator (or designee) is responsible for contacting the Principal Investigator (or designee).
4. The Principal Investigator (or designee) is responsible for reviewing and approving all requests for unblinding. Once approved, the Research Coordinator (or designee) will provide the site with the participant's treatment allocation. This information is to be provided by telephone. No information regarding treatment allocation is to be sent via email or fax.
5. The unblinded FAITH-2 personnel are not to unblind the Principal Investigator or any blinded members of the FAITH-2 team unless deemed necessary by the Principal Investigator.
6. FAITH-2 personnel must keep all information related to the individual unblinding cases confidential.
7. All cases of unblinding must be documented, including; clinical site ID, study ID, date of unblinding, parties unblinded, and reason for unblinding.

Figure 7: Central Adjudication Process



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Fixation using Alternative Implants for the Treatment of Hip Fractures (FAITH-2):

A Multi-Centre 2x2 Factorial Randomized Trial Comparing Sliding Hip Screws versus Cancellous Screws AND Vitamin D versus Placebo on Patient Important Complications and Quality of Life in the Treatment of Young Adult (18-60) Femoral Neck Fractures

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Statistical Analysis Plan (SAP)

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26-Oct-2018	S. Sprague, S. Bzovsky	1.0	Initial version

Table of Contents

List of Tables

List of Figures

1.0 PURPOSE

The purpose of this statistical analysis plan (SAP) is to outline the primary statistical analyses for the Fixation using Alternative Implants for the Treatment of Hip Fractures (FAITH-2): A Multi-Centre 2x2 Factorial Randomized Trial Comparing Sliding Hip Screws versus Cancellous Screws AND Vitamin D versus Placebo on Patient Important Complications and Quality of Life in the Treatment of Young Adult (18-60) Femoral Neck Fractures manuscript. This SAP includes review of all data collected. The FAITH-2 Writing Committee will determine which data points will be included in the primary manuscript and supplemental documents. We will adhere to the CONSORT 2010 guideline when reporting the results of FAITH-2. Additional SAPs will be developed for secondary analyses.

2.0 STUDY SUMMARY

Title	**F**ixation using **A**lternative **I**mplants for the **T**reatment of **H**ip Fractures (FAITH-2): A Multi-Centre 2x2 Factorial Randomized Trial Comparing Sliding Hip Screws versus Cancellous Screws AND Vitamin D versus Placebo on Patient Important Outcomes and Quality of Life in the Treatment of Young Adult (18-60) Femoral Neck Fractures
Short Title	FAITH-2
Methodology	Concealed 2x2 factorial randomized controlled trial
Clinical Sites	Multiple international clinical sites
Primary Objective	The primary objective is to assess the impact of surgical implant (sliding hip screws (SHS) versus cancellous screw (CS) fixation) *AND* nutritional supplementation (vitamin D versus placebo) on a composite of patient important outcomes during the 12 month post-surgery follow-up period. The composite of patient important outcomes includes: re-operation, femoral head osteonecrosis, severe femoral neck malunion, and nonunion.
Secondary Objectives	To assess the impact of surgical implant (sliding hip screw fixation versus cancellous screw fixation) and nutritional supplementation (vitamin D versus placebo) on health-related quality of life and functional outcomes, fracture healing complications, and radiographic fracture healing.
Sample Size	We will recruit a sample size of 808 patients with full follow-up. Based on an anticipated 10% loss to follow-up, 898 patients will need to be enrolled in the FAITH-2 trial.
Diagnosis and Main Inclusion Criteria	Femoral neck fracture in patients between the ages of 18 and 60.
Study Products	Surgical implants: Sliding hip screw versus multiple cancellous screws. Nutritional supplementation: Vitamin D_3 (4,000 International Units/day taken for 6 months) versus placebo taken for 6 months.
Length of Follow-Up	12 months.

3.0 SCREENING AND ENROLMENT

The number of participants screened, included, and excluded will be presented in separate flow diagrams by surgical treatment and nutritional supplementation groups (**Figures 1 and 2**). The figure will include the number of patients who were eligible, ineligible, and randomly assigned to the two treatment groups. It will also include the number of participants who are lost to follow-up over the course of the study. The number of patients excluded by reason will be summarized in **Table 1**.

Figure 1: Flow Diagram – Surgical Treatment

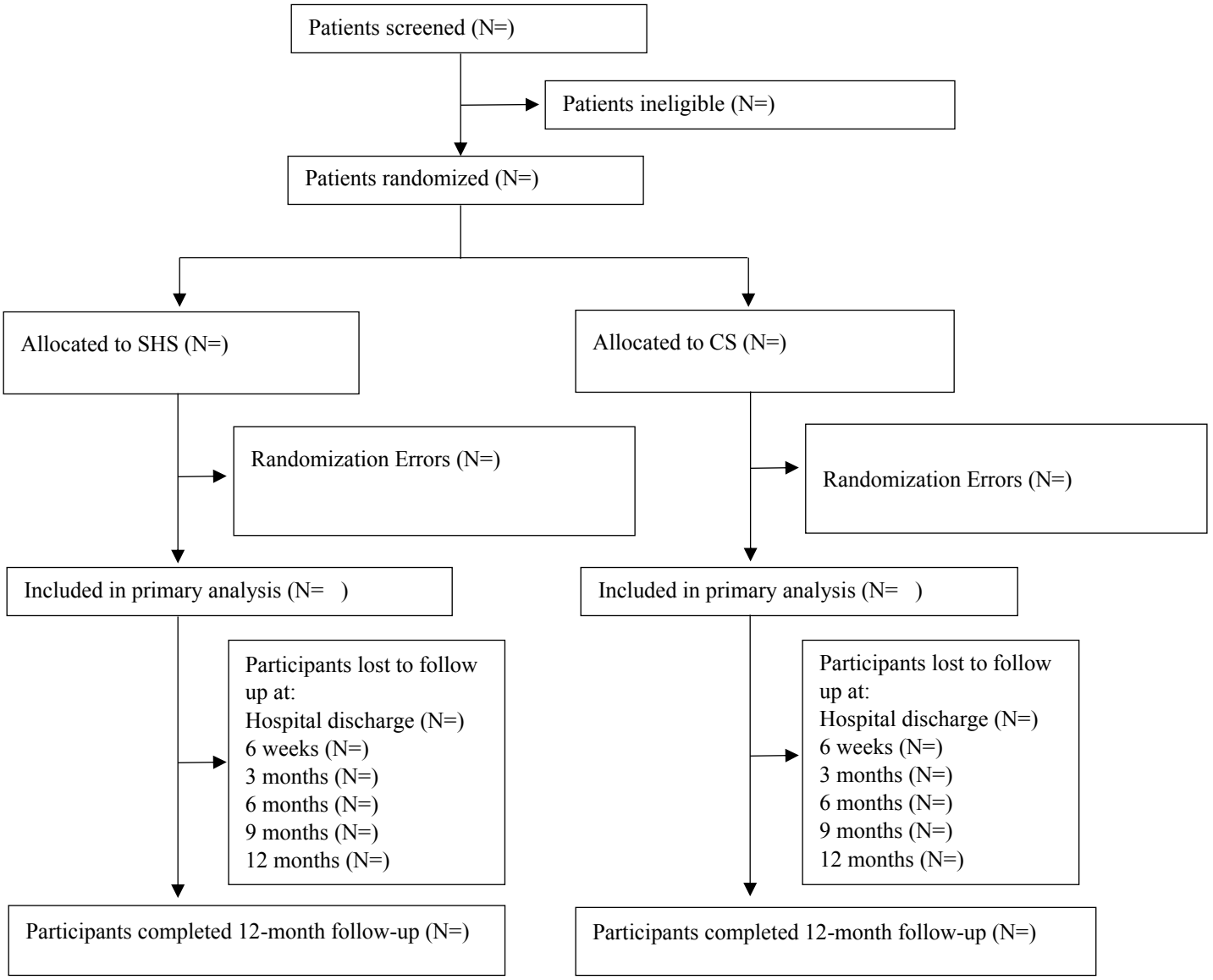


Figure 2: Flow Diagram – Nutritional Supplementation

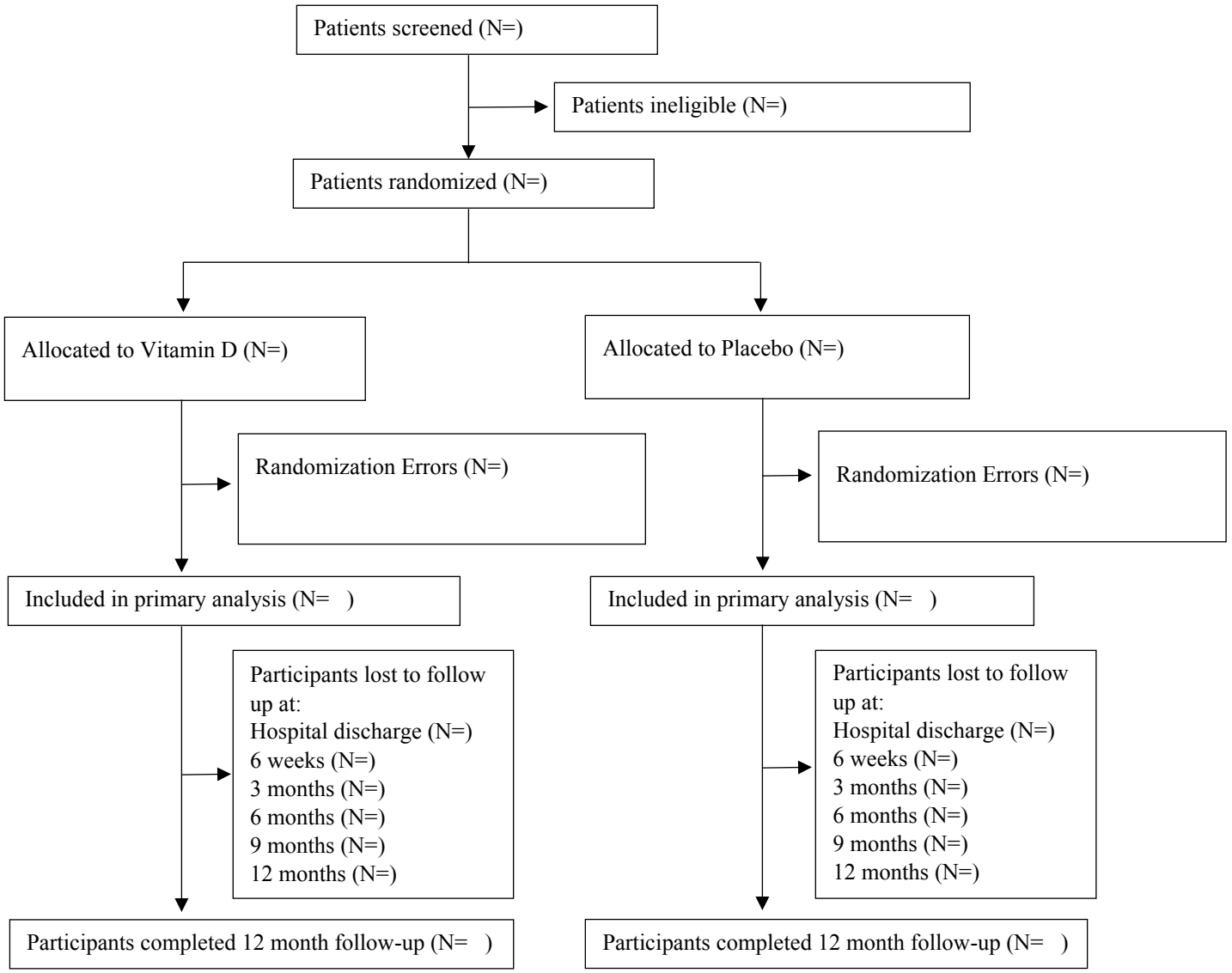


Table 1: Reasons for Exclusion at Screening

Reasons for Exclusion	Number of Patients N=	Number of Patients Excluded Due to Randomization Errors				
		Surgical Treatment X N=	Surgical Treatment Y N=	Nutritional Supplementation X N=	Nutritional Supplementation Y N=	Total N=
Inclusion Criteria						
The patient is not between the ages of 18 and 60 years						
The patient does not have a femoral neck fracture						
The fracture is not amenable to both surgical treatments (SHS and cancellous screw)						
Operative treatment will not take place within 7 days of injury						
Exclusion Criteria						
The patient has previously been diagnosed with osteoporosis						
The patient has a fracture-dislocation of the femoral neck and hip joint						
The patient has planned antegrade nailing of an ipsilateral femoral shaft fracture (if present)						
The patient has an infection around the hip (i.e. soft tissue or bone)						
The patient has a stress fracture of the femoral neck						
This is a pathological fracture secondary to neoplasm or other bone lesion						
The patient has a known or likely undiagnosed disorder of bone metabolism such as Paget's disease, osteomalacia, osteopetrosis, osteogenesis imperfect, etc						
The patient is currently taking an over counter drug and/or food supplement that contains vitamin D and is unable or unwilling to discontinue its use for this study						
There are likely problems, in the judgement of the attending surgeon, with						

maintaining follow-up (e.g. patients with no fixed address, plans to move out of town). This may include patients with severe mental disorders and drug addictions without adequate support						
The patient is pregnant						
The patient is incarcerated						
The patient is not expected to survive their injuries						
The patient or substitute decision maker has not provided informed consent						
The patient is eligibile, but was not randomized due to error						

4.0 PARTICIPANT DEMOGRAPHICS CHARACTERISTICS

Participant demographic, baseline characteristics, and major comorbidities of the population will be summarized by surgical treatment and nutritional supplementation groups (**Table 2**). Descriptive statistics will be used to summarize the demographic data. Means and standard deviations (SDs) will be used for continuous data, and categorical data will be presented as frequencies and proportions.

Table 2: Participant Demographics

Characteristic	Variable	Surgical Treatment X N=43	Surgical Treatment Y N=43	Nutritional Supplementation X N=	Nutritional Supplementation Y N=	Total N=86
Age, mean (SD) (years)	2.1 Q5, 3.1 Q1					
Sex, n (%) Male Female	3.1 Q2					
Ethnicity, n (%) Native/Aboriginal South Asian East Asian Southeast Asian (Filipino) Hispanic/Latino White/Caucasian Black (African/Caribbean) Mixed (Black & White) Middle Eastern	3.1 Q3					

Characteristic	Variable	Surgical Treatment X N=43	Surgical Treatment Y N=43	Nutritional Supplementation X N=	Nutritional Supplementation Y N=	Total N=86
Body Mass Index (BMI) (kg/m^2), n (%) Underweight <18.5 Normal weight 18.5-24.9 Overweight 25-29.9 Obese 30-39.9 Morbidly Obese ≥40	3.1 Q4, Q5					
Work-Related Injury, n (%)	3.1 Q7					
History of Smoking, n (%) Yes Previously smoked but quit No	3.1 Q8					
Consumption of Alcohol, n (%)	3.1 Q9					
Current Medications, n (%) None Nonsteroidal Anti-Inflammatory Drugs Steroid Medications Calcium Vitamin D	3.2 Q11					
Major Comorbidities, n (%) None One Two Three Four Five	3.2 Q12					

5.0 INJURY AND FRACTURE CHARACTERISTICS

Injury details and fracture characteristics will be summarized in **Table 3**. Pre-operative and post-operative care details (**Table 4**) will be presented for each surgical treatment and nutritional supplementation group. Means and SDs will be used for continuous data, and categorical data will be presented as frequencies and proportions.

Table 3: Fracture Characteristics

Characteristic	Variable	Surgical Treatment X N=	Surgical Treatment Y N=	Nutritional Supplementation X N=	Nutritional Supplementation Y N=	Total N=
Level of the Fracture Line, n (%) Subcapital Midcervical Basal Unable to assess	Adjudicated Data					
Garden Classification, n (%) Garden I (undisplaced) Garden II (undisplaced) Garden III (displaced) Garden IV (displaced) Unable to assess	Adjudicated Data					
Pauwels' Classification, n (%) Type I Type II Type III Unable to assess	Adjudicated Data					
Mechanism of Injury, n (%) Motor Vehicle Accident (Driver/Passenger) Motor Vehicle Accident (Pedestrian) Motorcycle Accident Recreational Vehicle (4 Wheeler, Snowmobile, ATV, etc) Bicycle Accident Fall from Height (>1m) Fall from Height (≤1m) Fall from Standing Direct Trauma (Blunt) Direct Trauma (Penetrating)	3.3 Q15					
Additional Fractures, n (%) Upper extremity Lower extremity Spine and sacrum Pelvis	3.4 Q20					
Additional Injuries, n (%) Chest Injury Abdominal Injury Head/Neck Injury Soft Tissue Injuries to Extremities	3.4 Q24					

Characteristic	Variable	Surgical Treatment X N=	Surgical Treatment Y N=	Nutritional Supplementation X N=	Nutritional Supplementation Y N=	Total N=
Ipsilateral Femoral Shaft Fracture, n (%)	3.5 Q23					

Table 4: Summary of Pre-Operative and Post-Operative Care Details

Characteristic	Variable	Surgical Treatment X N=	Surgical Treatment Y N=	Nutritional Supplementation X N=	Nutritional Supplementation Y N=	Total N=
Pre-operative Antibiotic Prophylaxis, n (%)	3.5 Q26					
Discharge Location, n (%) Home Rehabilitation Facility Other Hospital Medical Respite	7.1 Q2					
Provided with Nutritional Supplement, n (%)	7.1 Q3					
Received Nutritional Supplement Within Two Weeks of Femoral Neck Surgery, n (%)	7.1 Q5					
Nutritional Instructions and Importance of Complying with Nutritional Supplementation Discussed with Participant, n (%)	7.1 Q6					

6.0 SUMMARY OF SURGICAL PROCEDURES

The following sections will summarize the surgical procedures. General surgical characteristics and the surgical details for each surgical treatment and nutritional supplementation group will be presented. Means with SDs will be used for continuous data, and categorical data will be presented as frequencies and proportions (**Tables 5, 6, and 7**).

Table 5: General Surgical Characteristics

Surgery Characteristic	Variable	Surgical Treatment X N=	Surgical Treatment Y N=	Nutritional Supplementation X N=	Nutritional Supplementation Y N=	Total N=
Time from Injury to Surgery, mean (SD) (hours)	3.3 Q13, 4.1 Q1/Q2					
Length of Procedure, mean (SD) (minutes)	4.1 Q2/Q3					
Attending Surgeon Present in Operating Room for Critical Aspects of Procedure, n (%)	4.1 Q5					

Surgery Characteristic	Variable	Surgical Treatment X N=	Surgical Treatment Y N=	Nutritional Supplementation X N=	Nutritional Supplementation Y N=	Total N=
Who Performed Majority of Procedure, n (%) Surgeon Fellow Resident	4.1 Q6					
Total Blood Loss, mean (SD) (mL)	4.1 Q7					
Type of Reduction Used, n (%) Closed Open None	4.1 Q8					
Procedure Performed, n (%) CS SHS Cephalomedullary Nail	4.1 Q9					
Implant Manufacturer, n (%) Synthes Biomet Stryker Smith & Nephew DePuy Hansson Zimmer	4.1 Q10					
Capsulotomy Performed, n (%)	4.2 Q11					
Aspiration of Intracapsular Hematoma, n (%)	4.2 Q12					
Additional Buttress-type Plates Used, n (%)	4.2 Q13					
Injectable Bone Substitutes Used, n (%)	4.2 Q14					
Bone Graft Used, n (%)	4.2 Q15					
Other Procedures Performed During Same Operation as Femoral Neck Fracture Internal Fixation, n (%)	4.2 Q16					
Treatment of Ipsilateral Femoral Neck Fracture, n (%) N/A (No Ipsilateral Shaft Fracture) Plating Retrograde Nailing Antegrade Nailing	4.2 Q18					
Re-operations Planned For Patient's Fractured Hip, n (%) Irrigation and Debridement Wound Closure Implant Revision Implant Exchange Implant Adjustment	4.3 Q19					

Surgery Characteristic	Variable	Surgical Treatment X N=	Surgical Treatment Y N=	Nutritional Supplementation X N=	Nutritional Supplementation Y N=	Total N=
Bone Graft Femoral Shaft Fracture Surgery						

Table 6: CS Surgical Management

*to be completed only after unblinding

CS Characteristic	Variable	CS N=
Number of Screws Used, n (%) Three Four	5.1 Q2	
Diameter of Screws, mean (SD) (mm)	5.1 Q3	
Number of Partially Threaded Screws with Short Threads Used, n (%) Zero One Two Three Four	5.1 Q4	
Number of Partially Threaded Screws with Long Threads Used, n (%) Zero One Two Three Four	5.1 Q5	
Formation of Screws (or Pins), n (%) Triangle (Apex at Top) (3 Screws) Inverted Triangle (Apex at Bottom) (3 Screws) Square (4 Screws) Diamond (4 Screws) Other	5.1 Q6	
Aiming of Screws (or Pins), n (%) Parallel Crossed	5.1 Q7	
Number of Washers Used, n (%) Zero One Two Three Four	5.1 Q8	
Use of Hook Pins or Any Other Non-Screw Implants, n (%)	5.1 Q9	

Table 7: SHS Surgical Management

*to be completed only after unblinding

SHS Characteristic	Variable	SHS N=
Type of Sliding Fixed-Angle Plate Construct Used, n (%) Traditional Large Diameter Hip Screw Spiral/Helical Blade Dynamic Hip Screw	6.1 Q2	
Implant Position in Head of Femur, n (%) Centre-Centre Position Superior Position Anterior Position Inferior Position Posterior Position Other (specify):	6.1 Q3	
Number of Holes in Side Plate, n (%) Two Three Four	6.1 Q4	
Number of Cortical Screws in Side Plate, n (%) Two Three Four	6.1 Q5	
Supplemental (Derotational) Screws Included in Fixation, n (%) With Washer Without Washer	6.1 Q6	
Used of Compression Screw, n (%)	6.1 Q7	
Final Tip Apex Distance, mean (SD) (mm)	6.1 Q8	

7.0 FEASIBILITY OUTCOME MEASURES

Feasibility outcomes will be analyzed using descriptive statistics, reported as count and percentage or mean and standard deviation depending on the type of variable to summarize the FAITH-2 feasibility outcomes of 1) initiation of clinical sites (locations and timelines), 2) rate of participant enrolment, 3) rate of protocol adherence (the number of errors in randomization, 4) the number of crossovers between SHS and cancellous screw treatment groups, 5) adherence to the daily vitamin D supplementation), 6) proportion of participants with complete follow-up at 12 months post-fracture, 7) and level of data quality (**Table 8**).

Table 8: Feasibility Outcomes

Feasibility Outcomes	Variable	N=
Time to Initiation of Clinical Sites, median (IQR) (months)	Clinical site initiation tracker	
Time to Enroll 60 Participants, n (months)	2.1 Q5 of first and last enrolled participant	
Rate of Protocol Adherence: Number of Errors in Randomization, n (%)	14.1 Q2	
Rate of Protocol Adherence: Number of Crossovers between SHS and CS treatment groups, n (%)	5.1 Q1, 6.1 Q1	
Rate of Protocol Adherence: Adherence to the daily vitamin D supplementation, n (%)	8.2 Q10/Q11 (6 weeks, 3 months, 6 months)	
Proportion of Participants with Complete Follow-up at 12 Months Post-Fracture, n (%)	8.1 (12 months)	
Level of Data Quality, n (%)	Completeness of CRFs	

8.0 PRIMARY CLINICAL ENDPOINT

The primary analyses will first be completed using only blinded treatment groups. All outcome analyses will be performed using the intention to treat approach. The FAITH-2 study primary clinical endpoint is a composite of patient important outcomes that occur within the 12 months post-surgery follow-up period (**Table 9**). Specifically, these are limited to 1) re-operation, 2) femoral head osteonecrosis, 3) severe femoral neck malunion, and 4) nonunion.

The first analysis of clinical outcomes will be a Cox regression with main effects for implant type and supplementation, and the interaction between the two. If the interaction is not significant at alpha=0.05 we will perform two independent comparisons between the treatment groups (SHS versus cancellous screws AND separately vitamin D_3 supplementation versus placebo) using the chi-square statistic and an alpha level of 0.05 for the composite of patient important outcomes (**Tables 10 and 11**).

If the interaction is significant we will keep this interaction term in all subsequent analyses, and present two hazard ratios (HRs) with 95% confidence intervals (CIs) for the surgical intervention and two HRs for the nutritional supplementation (i.e. We will report an HR for SHS versus cancellous screws in those who receive vitamin D, and a separate HR for SHS versus cancellous screws in those who receive placebo. We will also report an HR for vitamin D versus placebo in those who receive SHS, and a separate HR for vitamin D versus placebo in those who receive cancellous screws) The results will be summarized in **Table 12**. Kaplan-Meier curves will also be constructed.

Table 9: Primary Clinical Endpoint Components and Reasons for Secondary Procedures

Outcome	Definition
Unplanned Secondary Procedures (study event)	Any unplanned surgery related to the treatment of the femoral neck fracture. Specific unplanned secondary procedures include: • Implant removal • Bone graft • Wound closure • Proximal femur osteotomy • Implant exchange – THA • Implant exchange – HA • Implant exchange – CS • Implant exchange – SHS • Implant exchange – Other IF • Soft tissue procedure • Dynamization • Osteochondroplasty
Reasons for Secondary Procedures	• Shortening • Nonunion • Femoral head osteonecrosis • Deep infection • Superficial infection • Painful implant • Implant failure/breakage • Hip dislocation • Peri-prosthetic femur fracture • Hip instability • Wound healing problem • Screw penetration • Screw cut-out • Post traumatic arthritis • IT Fracture • Relieve pain
Femoral Head Necrosis	Any evidence of osteonecrosis on any follow-up medical imaging study (i.e., radiographs, magnetic resonance imaging (MRI), or other advanced imaging study)
Severe Femoral Neck Malunion	Fracture healing with femoral neck shortening of >10 mm in any plane on follow-up x-rays[1]
Nonunion	Failure of the fracture to progress towards healing defined as a Radiographic Union Score for Hip (RUSH)[2,3] score below a pre-determined threshold specific for nonunion at 6 months or greater post-injury.

Table 10: Primary Clinical Endpoint, According to Surgical Treatment (No Significant Interaction Between Implant Type and Supplementation Present)

End Point	Variable	Overall N=	Surgical Treatment X N=	Surgical Treatment Y N=	P-Value
Primary Clinical Endpoint of Re-operation					
Re-operation	Adjudicated Data				
Procedure for Nonunion Implant removal Bone graft Proximal femur osteotomy Implant exchange – THA Implant exchange – IF	Adjudicated Data				
Procedure for Femoral Head Osteonecrosis Implant removal Implant exchange – THA	Adjudicated Data				
Procedure for Deep Infection Wound closure Implant exchange – SHS Soft tissue procedure	Adjudicated Data				
Procedure for Painful Hardware Implant removal Bone graft Implant exchange – THA	Adjudicated Data				
Procedure for Screw Penetration Implant removal	Adjudicated Data				
Procedure for Post-Traumatic Arthritis Osteochondroplasty	Adjudicated Data				
Procedure for IT Fracture Implant exchange – IF	Adjudicated Data				
Procedure for Relieving Pain Implant exchange – THA	Adjudicated Data				
Femoral head osteonecrosis	Adjudicated Data				
Severe femoral neck malunion	Adjudicated Data				
Nonunion	Adjudicated Data				

Table 11: Primary Clinical Endpoint, According to Nutritional Supplementation (No Significant Interaction Between Implant Type and Supplementation Present)

End Point	Variable	Overall N=	Nutritional Supplementation X N=	Nutritional Supplementation Y N=	P-Value
Primary Clinical Endpoint of Re-operation					
Re-operation	Adjudicated Data				
Procedure for Nonunion Implant removal Bone graft Proximal femur osteotomy Implant exchange – THA Implant exchange – IF	Adjudicated Data				
Procedure for Femoral Head Osteonecrosis Implant removal Implant exchange – THA	Adjudicated Data				
Procedure for Deep Infection Wound closure Implant exchange – SHS Soft tissue procedure	Adjudicated Data				
Procedure for Painful Hardware Implant removal Bone graft Implant exchange – THA	Adjudicated Data				
Procedure for Screw Penetration Implant removal	Adjudicated Data				
Procedure for Post-Traumatic Arthritis Osteochondroplasty	Adjudicated Data				
Procedure for IT Fracture Implant exchange – IF	Adjudicated Data				
Procedure for Relieving Pain Implant exchange – THA	Adjudicated Data				
Femoral head osteonecrosis	Adjudicated Data				
Severe femoral neck malunion	Adjudicated Data				
Nonunion	Adjudicated Data				

Table 12: Primary Clinical Endpoint (Significant Interaction Between Implant Type and Supplementation Present)

End Point	Variable	Overall N=	Surgical Treatment X N=	Surgical Treatment Y N=	Nutritional Supplementation X N=	Nutritional Supplementation Y N=	Hazard Ratio (95% CI)				P-Value
							Surgery X + Supplement X vs. Surgery Y + Supplement X	Surgery X + Supplement Y vs. Surgery Y + Supplement Y	Surgery X + Supplement X vs. Surgery X + Supplement Y	Surgery Y + Supplement X vs. Surgery Y + Supplement Y	
Primary Clinical Endpoint: re-operation, femoral head osteonecrosis, severe femoral neck malunion, nonunion	Adjudicated Data										
Primary Clinical Endpoint Components											
Malunion Implant removal Bone graft Wound closure Proximal femur osteotomy Implant exchange – THA Implant exchange – HA Implant exchange – IF (crossover) Implant exchange – IF (original) Implant exchange – Intramedullary nailing Implant exchange – curved plate and IF Implant exchange – 110 degree blade plate Soft tissue procedure Dynamization Osteochondroplasty	Adjudicated Data										
Nonunion Implant removal	Adjudicated Data										

Bone graft Wound closure Proximal femur osteotomy Implant exchange – THA Implant exchange – HA Implant exchange – IF (crossover) Implant exchange – IF (original) Implant exchange – Intramedullary nailing Implant exchange – curved plate and IF Implant exchange – 110 degree blade plate Soft tissue procedure Dynamization Osteochondroplasty											
Femoral Head Osteonecrosis Implant removal Bone graft Wound closure Proximal femur osteotomy Implant exchange – THA Implant exchange – HA Implant exchange – IF (crossover) Implant exchange – IF (original) Implant exchange – Intramedullary nailing Implant exchange – curved plate and IF Implant exchange –	Adjudicated Data										

110 degree blade plate Soft tissue procedure Dynamization Osteochondroplasty											
Deep Infection Implant removal Bone graft Wound closure Proximal femur osteotomy Implant exchange – THA Implant exchange – HA Implant exchange – IF (crossover) Implant exchange – IF (original) Implant exchange – Intramedullary nailing Implant exchange – curved plate and IF Implant exchange – 110 degree blade plate Soft tissue procedure Dynamization Osteochondroplasty	Adjudicated Data										
Superficial Infection Implant removal Bone graft Wound closure Proximal femur osteotomy Implant exchange – THA Implant exchange – HA Implant exchange – IF (crossover) Implant exchange – IF (original)	Adjudicated Data										

Implant exchange – Intramedullary nailing Implant exchange – curved plate and IF Implant exchange – 110 degree blade plate Soft tissue procedure Dynamization Osteochondroplasty											
Painful Hardware Implant removal Bone graft Wound closure Proximal femur osteotomy Implant exchange – THA Implant exchange – HA Implant exchange – IF (crossover) Implant exchange – IF (original) Implant exchange – Intramedullary nailing Implant exchange – curved plate and IF Implant exchange – 110 degree blade plate Soft tissue procedure Dynamization Osteochondroplasty	Adjudicated Data										
Hardware Failure/Breakage Implant removal Bone graft Wound closure Proximal femur osteotomy Implant exchange – THA	Adjudicated Data										

Implant exchange – HA Implant exchange – IF (crossover) Implant exchange – IF (original) Implant exchange – Intramedullary nailing Implant exchange – curved plate and IF Implant exchange – 110 degree blade plate Soft tissue procedure Dynamization Osteochondroplasty											
Hip Dislocation Implant removal Bone graft Wound closure Proximal femur osteotomy Implant exchange – THA Implant exchange – HA Implant exchange – IF (crossover) Implant exchange – IF (original) Implant exchange – Intramedullary nailing Implant exchange – curved plate and IF Implant exchange – 110 degree blade plate Soft tissue procedure Dynamization Osteochondroplasty	Adjudicated Data										
Peri-prosthetic Femur Fracture Implant removal	Adjudicated Data										

Bone graft Wound closure Proximal femur osteotomy Implant exchange – THA Implant exchange – HA Implant exchange – IF (crossover) Implant exchange – IF (original) Implant exchange – Intramedullary nailing Implant exchange – curved plate and IF Implant exchange – 110 degree blade plate Soft tissue procedure Dynamization Osteochondroplasty											
Hip Instability Implant removal Bone graft Wound closure Proximal femur osteotomy Implant exchange – THA Implant exchange – HA Implant exchange – IF (crossover) Implant exchange – IF (original) Implant exchange – Intramedullary nailing Implant exchange – curved plate and IF Implant exchange – 110 degree blade plate	Adjudicated Data										

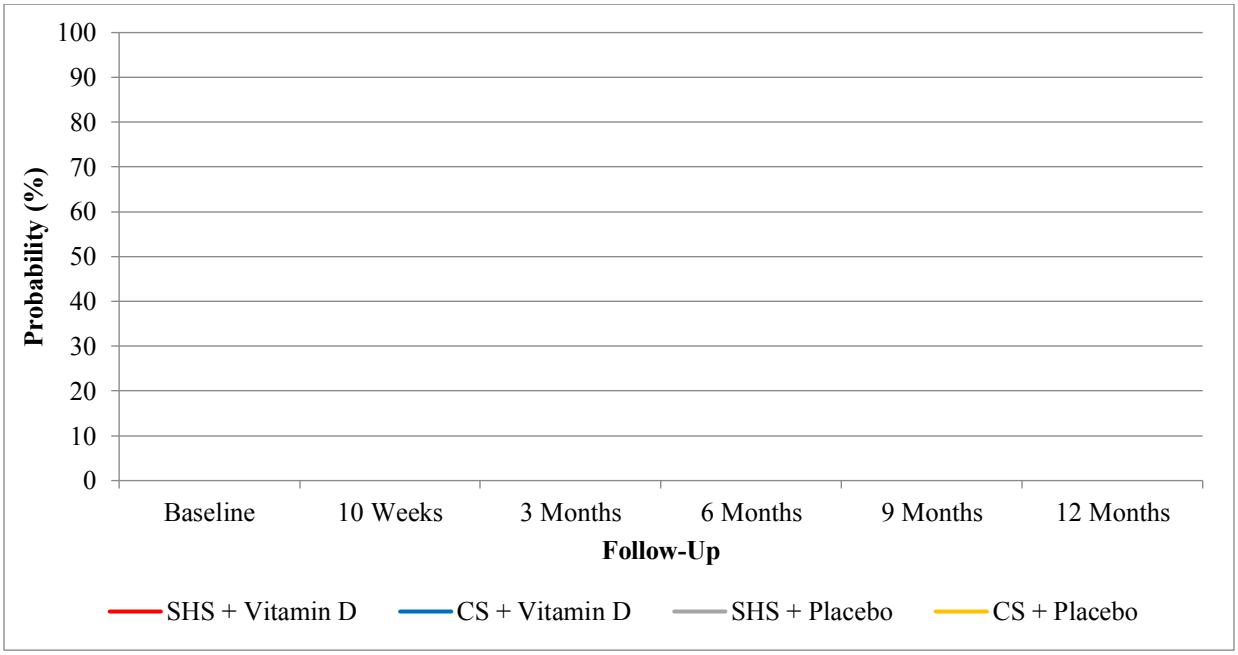
Soft tissue procedure Dynamization Osteochondroplasty											
Wound Healing Implant removal Bone graft Wound closure Proximal femur osteotomy Implant exchange – THA Implant exchange – HA Implant exchange – IF (crossover) Implant exchange – IF (original) Implant exchange – Intramedullary nailing Implant exchange – curved plate and IF Implant exchange – 110 degree blade plate Soft tissue procedure Dynamization Osteochondroplasty	Adjudicated Data										
Screw Penetration Implant removal Bone graft Wound closure Proximal femur osteotomy Implant exchange – THA Implant exchange – HA Implant exchange – IF (crossover) Implant exchange – IF (original) Implant exchange –	Adjudicated Data										

Intramedullary nailing Implant exchange – curved plate and IF Implant exchange – 110 degree blade plate Soft tissue procedure Dynamization Osteochondroplasty											
Screw Cut-Out Implant removal Bone graft Wound closure Proximal femur osteotomy Implant exchange – THA Implant exchange – HA Implant exchange – IF (crossover) Implant exchange – IF (original) Implant exchange – Intramedullary nailing Implant exchange – curved plate and IF Implant exchange – 110 degree blade plate Soft tissue procedure Dynamization Osteochondroplasty	Adjudicated Data										
Post-Traumatic Arthritis Implant removal Bone graft Wound closure Proximal femur osteotomy Implant exchange – THA Implant exchange – HA	Adjudicated Data										

Implant exchange – IF (crossover) Implant exchange – IF (original) Implant exchange – Intramedullary nailing Implant exchange – curved plate and IF Implant exchange – 110 degree blade plate Soft tissue procedure Dynamization Osteochondroplasty											
IT Fracture Implant removal Bone graft Wound closure Proximal femur osteotomy Implant exchange – THA Implant exchange – HA Implant exchange – IF (crossover) Implant exchange – IF (original) Implant exchange – Intramedullary nailing Implant exchange – curved plate and IF Implant exchange – 110 degree blade plate Soft tissue procedure Dynamization Osteochondroplasty	Adjudicated Data										
Relieve Pain Implant removal Bone graft Wound closure Proximal femur	Adjudicated Data										

osteotomy Implant exchange – THA Implant exchange – HA Implant exchange – IF (crossover) Implant exchange – IF (original) Implant exchange – Intramedullary nailing Implant exchange – curved plate and IF Implant exchange – 110 degree blade plate Soft tissue procedure Dynamization Osteochondroplasty											
Femoral Head Necrosis	Adjudicated Data										
Severe Femoral Neck Malunion	Adjudicated Data										
Nonunion	Adjudicated Data										

Figure 3: Kaplan-Meier Curves for Primary Clinical Endpoint (Significant Interaction Between Implant Type and Supplementation Present)



9.0 SECONDARY CLINICAL ENDPOINTS

The FAITH-2 secondary clinical endpoints include 1) health-related quality of life (HRQL), 2) patient-reported function, 3) fracture healing complications, and 4) radiographic fracture healing.

9.1 SF-12 Health Survey

The SF-12 Health Survey is a standardized instrument to measure health-related quality of life. This self-administered, 12-item questionnaire covers eight main health domains that make up the Physical and Mental Health Composite Scores (PCS & MCS). Each domain consists of one or two questions and is scored separately from 0 (lowest level) to 100 (highest level).[4] The SF-12 will be summarized using means and 95% CIs at 10-week, 3, 6, 9, and 12-month intervals (**Tables 13, 14, and 15**). Longitudinal models will be used to explore the effect of treatment group and time on the SF-12 patient-reported outcomes (**Figures 4-9**).

Table 13: HRQL (SF-12), According to Surgical Treatment (No Significant Interaction Between Implant Type and Supplementation Present)

Endpoint	Surgical Treatment X		Surgical Treatment Y		Total	
	N=	Mean (SD)	N=	Mean (SD)	N=	Adjusted Mean Difference (95% CI)
Physical Composite Scale (PCS) Scores						
Post-op						
10 weeks						
3 months						
6 months						
9 months						
12 months						
Mental Health Composite Scale (MCS) Scores						
Post-op						
10 weeks						
3 months						
6 months						
9 months						
12 months						

Table 14: HRQL (SF-12), According to Nutritional Supplementation (No Significant Interaction Between Implant Type and Supplementation Present)

Endpoint	Nutritional Supplementation Treatment X		Nutritional Supplementation Treatment Y		Total	
	N=	Mean (SD)	N=	Mean (SD)	N=	Adjusted Mean Difference (95% CI)
Physical Composite Scale (PCS) Scores						
Post-op						
10 weeks						
3 months						
6 months						
9 months						
12 months						
Mental Health Composite Scale (MCS) Scores						
Post-op						
10 weeks						
3 months						
6 months						
9 months						
12 months						

Figure 4: SF-12 PCS Scores Over Time by Surgical Treatment Group (No Significant Interaction Between Implant Type and Supplementation Present)

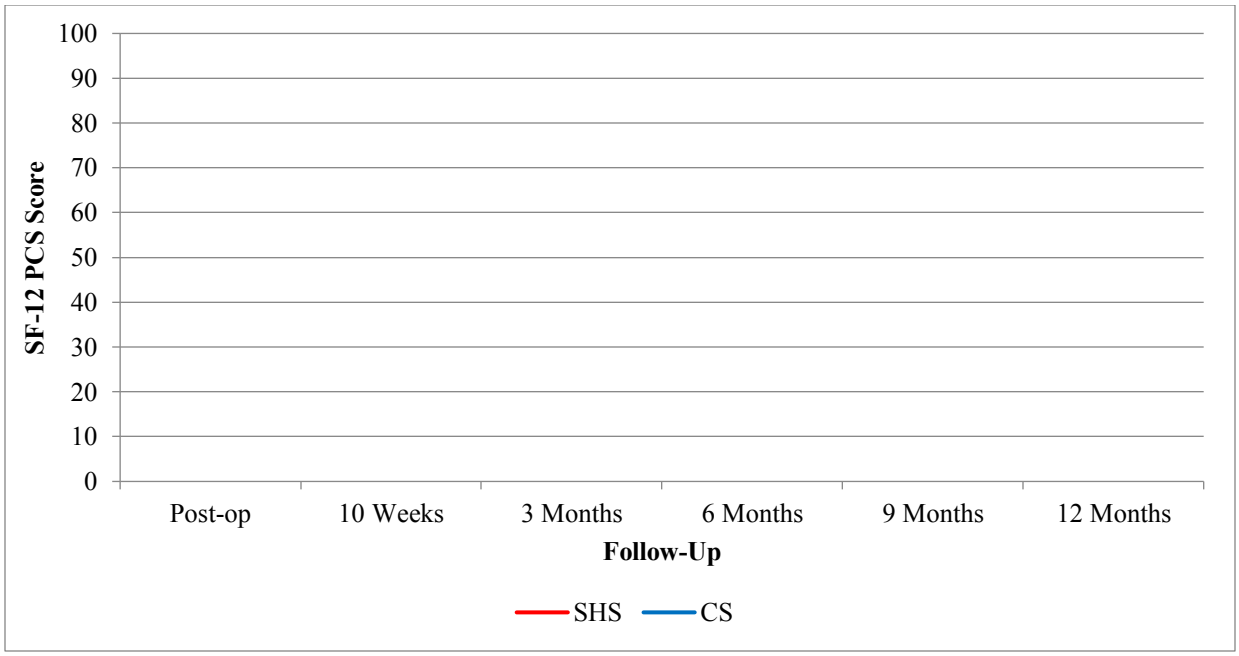


Figure 5: SF-12 MCS Scores Over Time by Surgical Treatment Group (No Significant Interaction Between Implant Type and Supplementation Present)

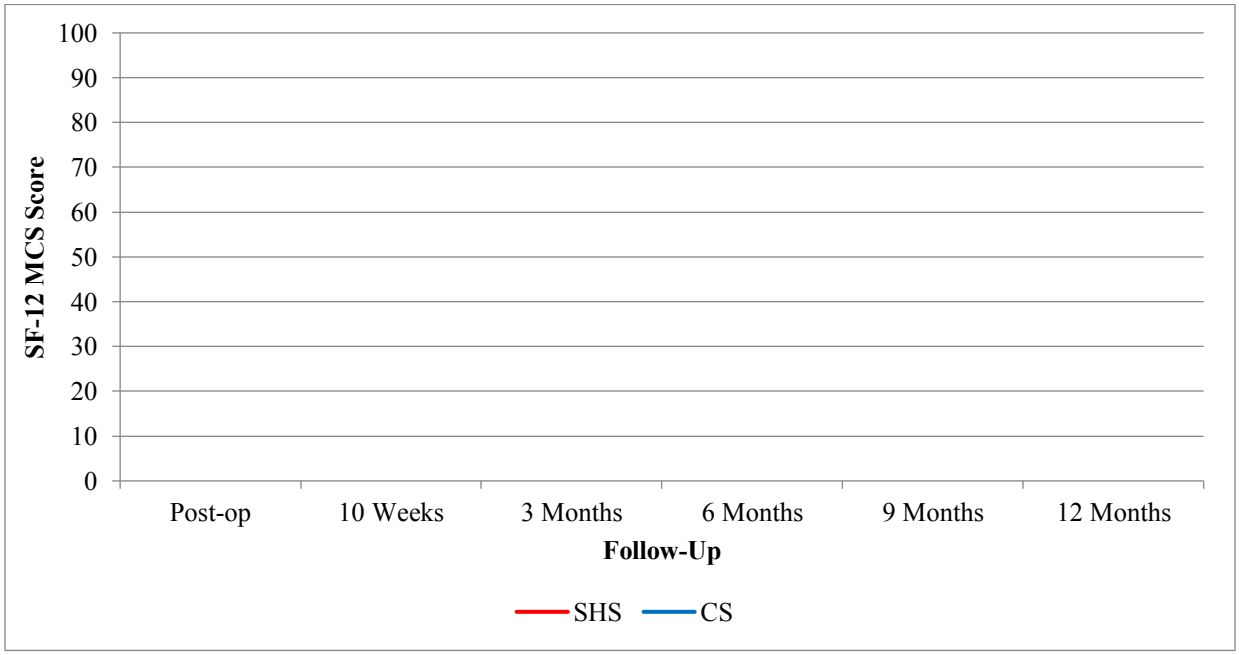


Figure 6: SF-12 PCS Scores Over Time by Nutritional Supplementation Group (No Significant Interaction Between Implant Type and Supplementation Present)

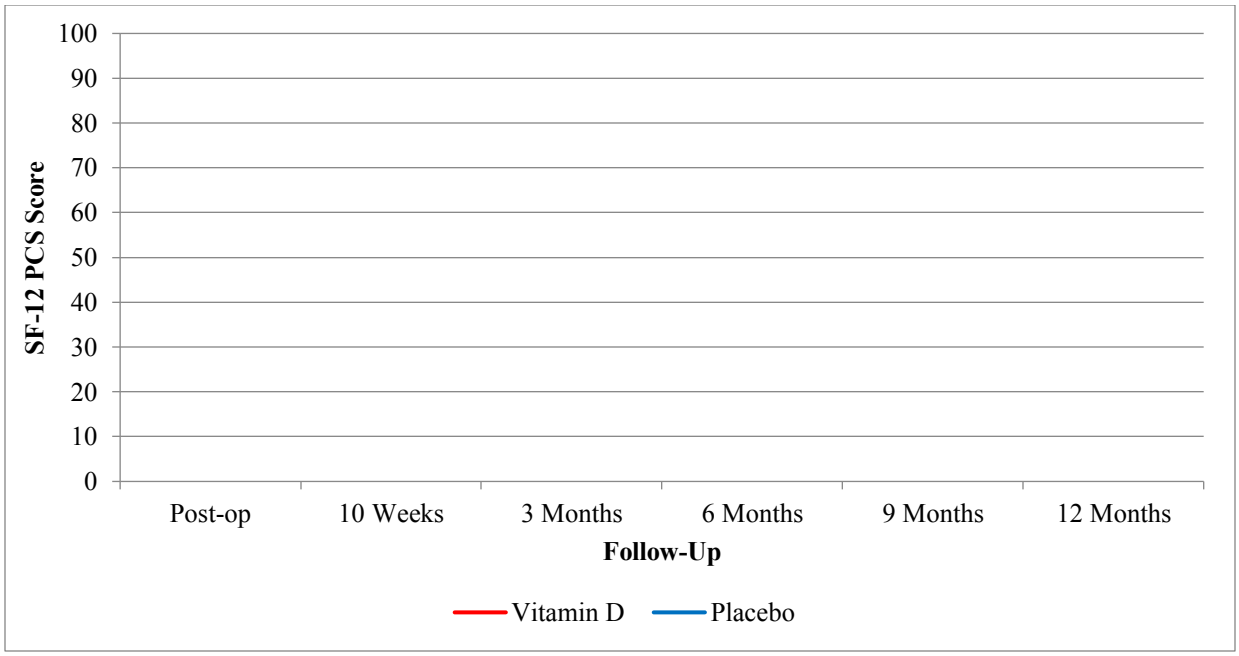


Figure 7: SF-12 MCS Scores Over Time by Nutritional Supplementation Group (No Significant Interaction Between Implant Type and Supplementation Present)

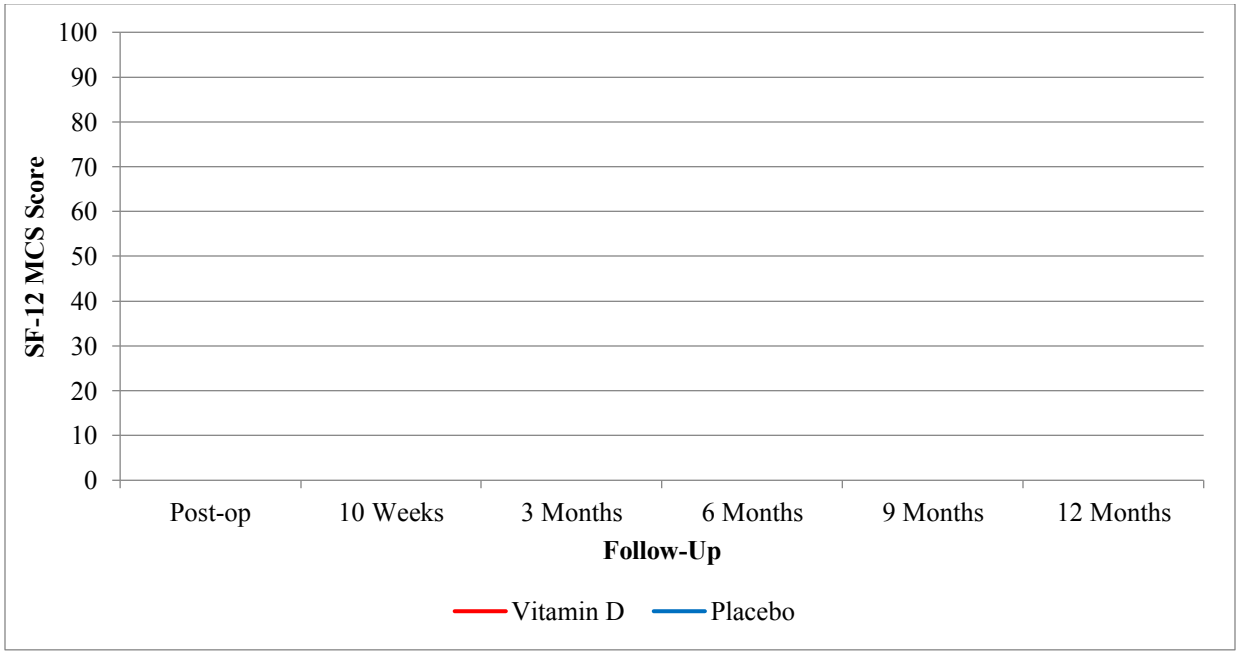


Table 15: HRQL (SF-12) (Significant Interaction Between Implant Type and Supplementation Present)

Endpoint	Surgical Treatment X		Surgical Treatment Y		Nutritional Supplementation Treatment X		Nutritional Supplementation Treatment Y		Total	
	N=	Mean (SD)	N=	Mean (SD)	N=	Mean (SD)	N=	Mean (SD)	N=	Adjusted Mean Difference (95% CI)
Physical Composite Scale (PCS) Scores										
Post-op										
10 weeks										
3 months										
6 months										
9 months										
12 months										
Mental Health Composite Scale (MCS) Scores										
Post-op										
10 weeks										
3 months										
6 months										
9 months										
12 months										

Figure 8: SF-12 PCS Scores Over Time by Treatment Group (Significant Interaction Between Implant Type and Supplementation Present)

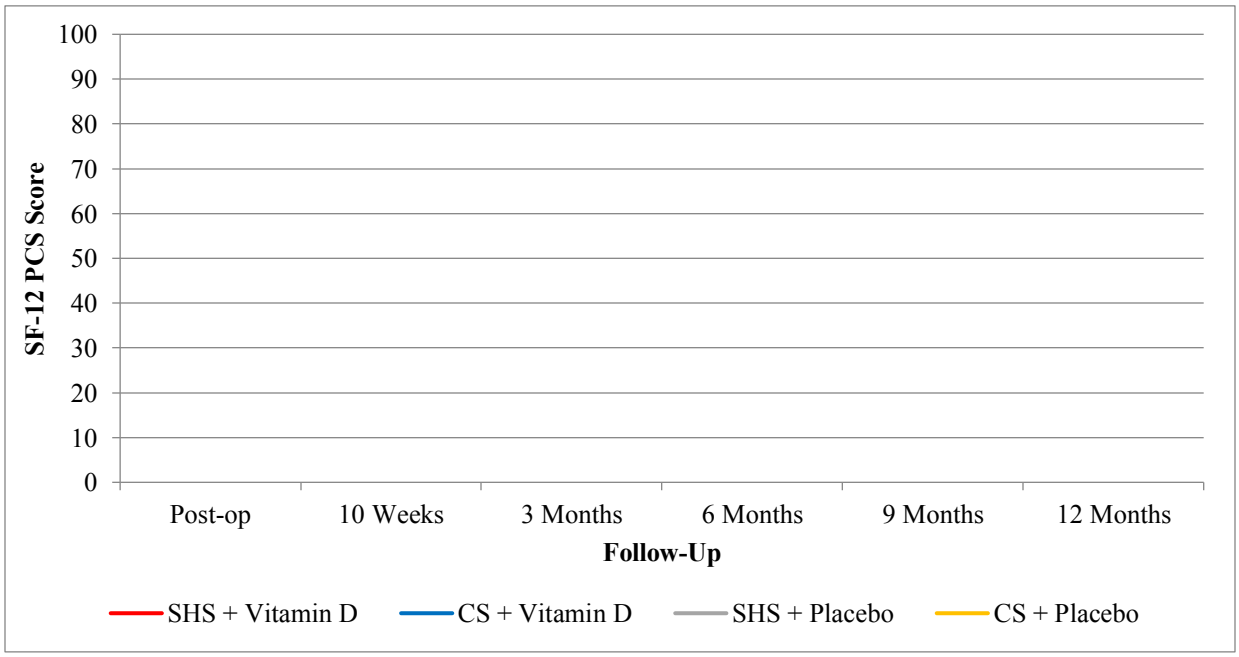
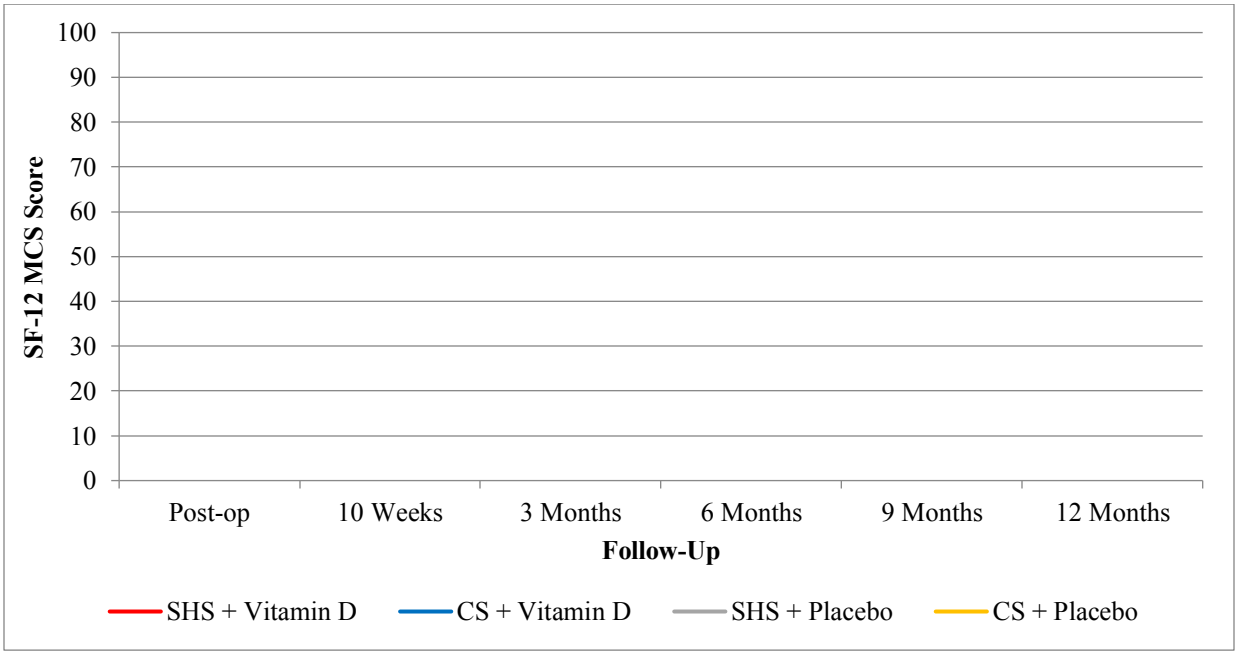


Figure 9: SF-12 MCS Scores Over Time by Treatment Group (Significant Interaction Between Implant Type and Supplementation Present)



9.2 Hip Outcome Score

The Hip Outcome Score (HOS)[5] measures self-reported functional status through 28 items and two sub-scales that pertain to activities of daily living (ADLs) or higher-level activities such as those necessary to participate in sports. Patient-reported function, measured by the HOS, will be reported as mean differences with corresponding 95% CIs and p-values. (**Tables 16, 17, and 18**). Longitudinal models will be used to explore the effect of treatment group and time on the HOS patient-reported outcomes (**Figures 10-12**).

Table 16: Summary of HOS, According to Surgical Treatment (No Significant Interaction Between Implant Type and Supplementation Present)

Endpoint	Surgical Treatment X		Surgical Treatment Y		Total	
	N=	Mean (SD)	N=	Mean (SD)	N=	Adjusted Mean Difference (95% CI)
Post-op						
10 weeks						
3 months						
6 months						
9 months						
12 months						

Table 17: Summary of HOS, According to Nutritional Supplementation (No Significant Interaction Between Implant Type and Supplementation Present)

Endpoint	Nutritional Supplementation Treatment X		Nutritional Supplementation Treatment Y		Total	
	N=	Mean (SD)	N=	Mean (SD)	N=	Adjusted Mean Difference (95% CI)
Post-op						
10 weeks						
3 months						
6 months						
9 months						
12 months						

Figure 10: HOS Over Time by Surgical Treatment Group (No Significant Interaction Between Implant Type and Supplementation Present)

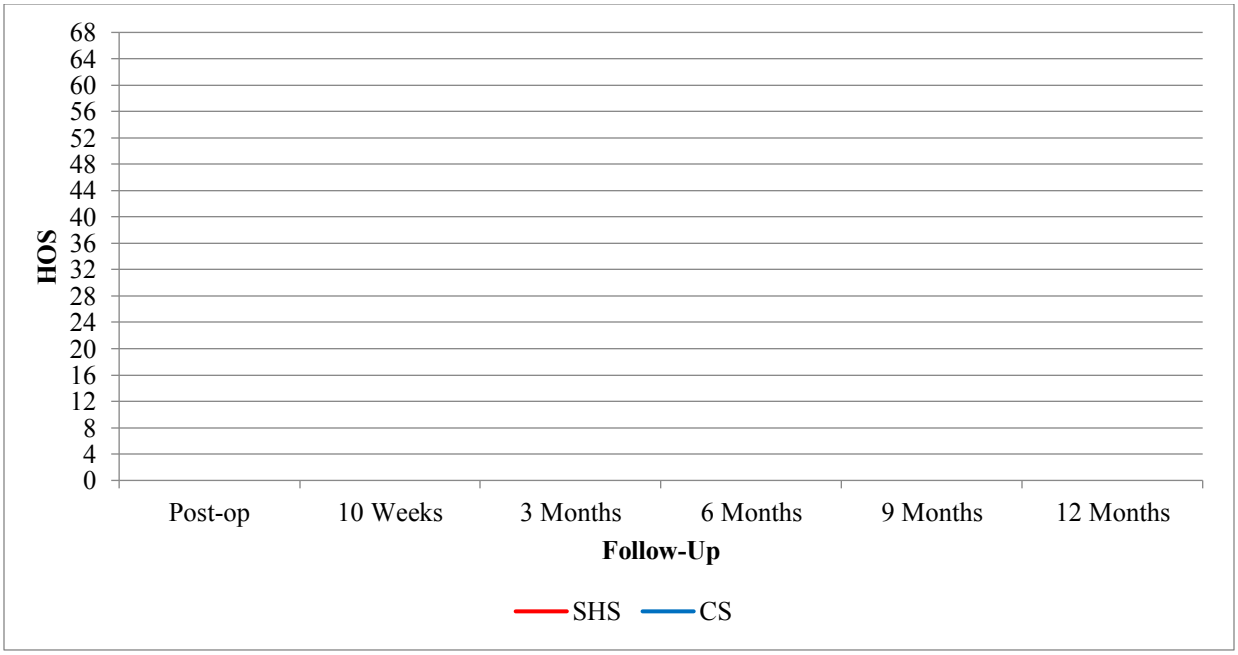


Figure 11: HOS Over Time by Nutritional Supplementation Group (No Significant Interaction Between Implant Type and Supplementation Present)

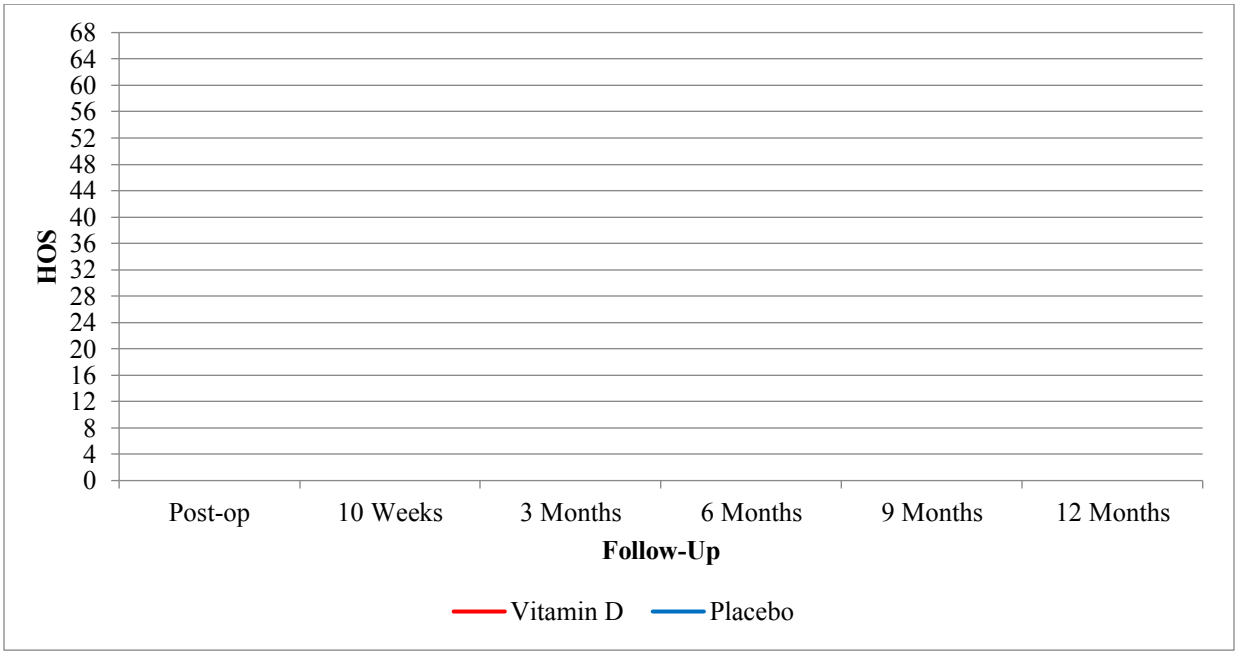
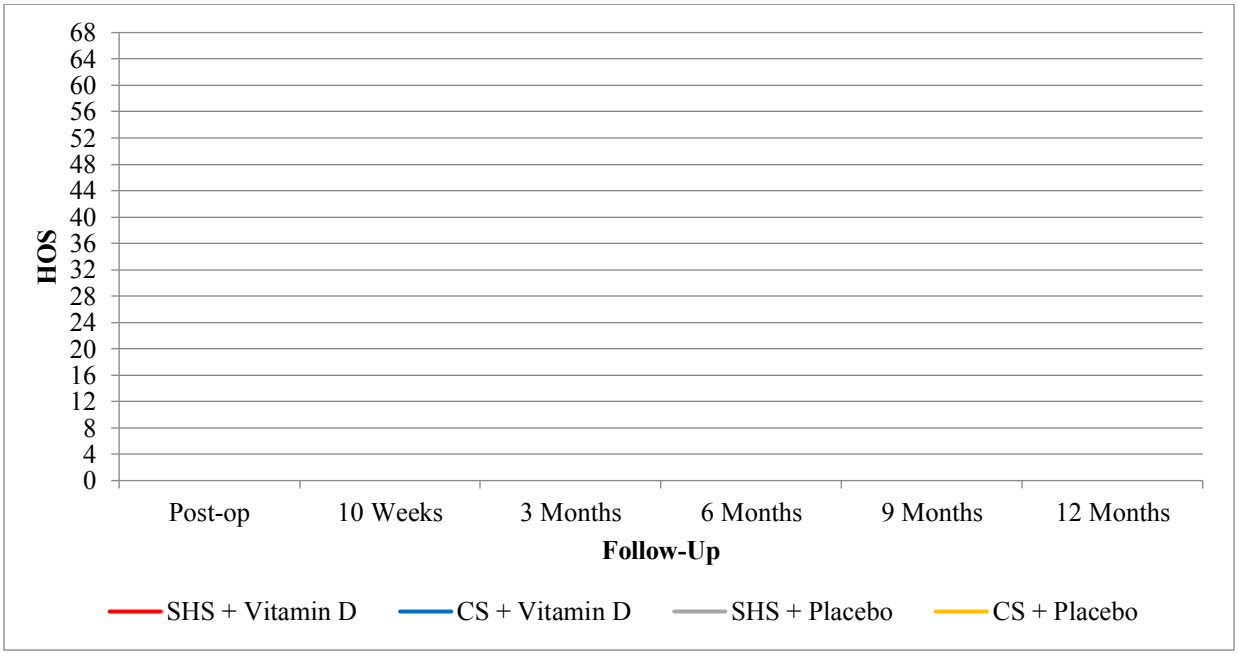


Table 18: Summary of HOS (Significant Interaction Between Implant Type and Supplementation Present)

Endpoint	Surgical Treatment X		Surgical Treatment Y		Nutritional Supplementation Treatment X		Nutritional Supplementation Treatment Y		Total	
	N=	Mean (SD)	N=	Mean (SD)	N=	Mean (SD)	N=	Mean (SD)	N=	Adjusted Mean Difference (95% CI)
Post-op										
10 weeks										
3 months										
6 months										
9 months										
12 months										

Figure 12: HOS Over Time by Treatment Group (Significant Interaction Between Implant Type and Supplementation Present)



9.3 Fracture Healing Complications

Table 19: Fracture Healing Complications

Fracture Healing Complication	Variable	Surgical Treatment X N=	Surgical Treatment Y N=	Nutritional Supplementation X N=	Nutritional Supplementation Y N=	Total N=
Wound Healing Problems	Adjudicated Data					
Infection - Superficial, n (%)	Adjudicated Data					
Infection – Deep, n (%)	Adjudicated Data					
Infection – Organ Space, n (%)	Adjudicated Data					
Implant Failure, n (%)	Adjudicated Data					
Implant Breakage, n (%)	Adjudicated Data					
Painful Hardware, n (%)	Adjudicated Data					
Peri-Prosthetic Fracture, n (%)	Adjudicated Data					
Other, n (%)	Adjudicated Data					

9.4 Radiographic Fracture Healing

Table 20: Radiographic Fracture Healing

Variable	Variable	Surgical Treatment X N=	Surgical Treatment Y N=	Nutritional Supplementation X N=	Nutritional Supplementation Y N=	Total N=
Time of Radiographic Fracture Healing, mean (SD) (months)	Adjudicated Data					
Time of Radiographic Healing of Ipsilateral Femoral Shaft Fracture, mean (SD) (months)	Adjudicated Data					

Figure 13: Kaplan-Meier Curves for Radiographic Fracture Healing (Significant Interaction Between Implant Type and Supplementation Present)

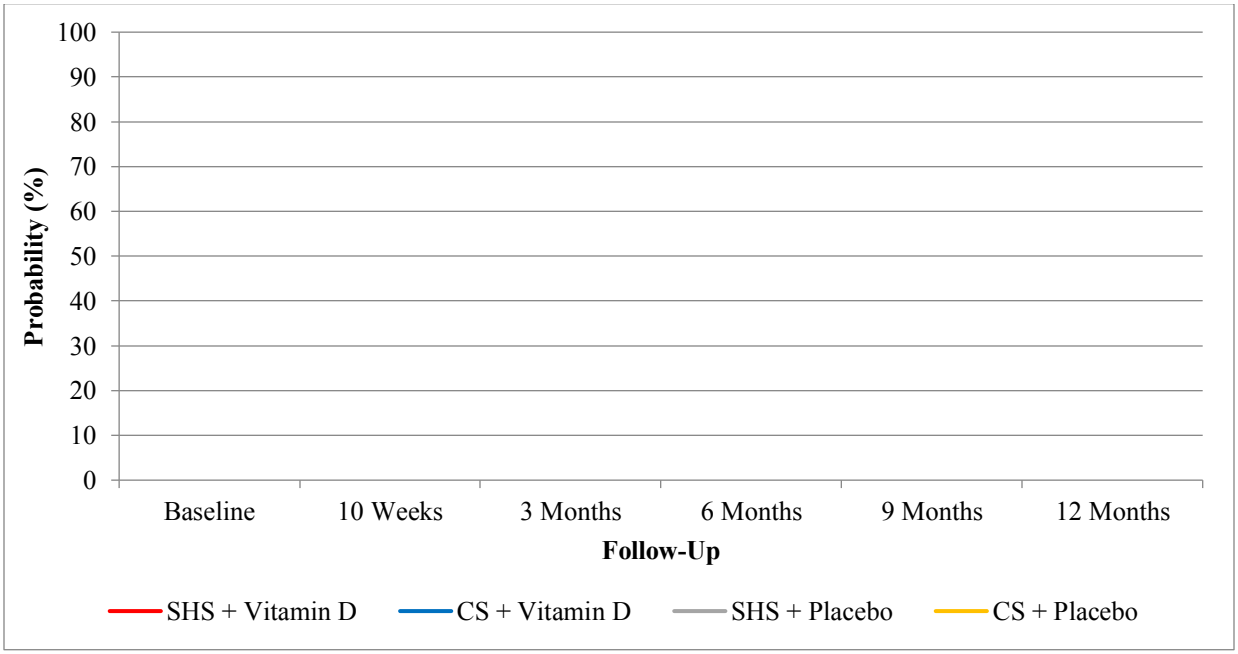


Figure 14: Kaplan-Meier Curves for Radiographic Fracture Healing by Surgical Treatment Group (No Significant Interaction Between Implant Type and Supplementation Present)

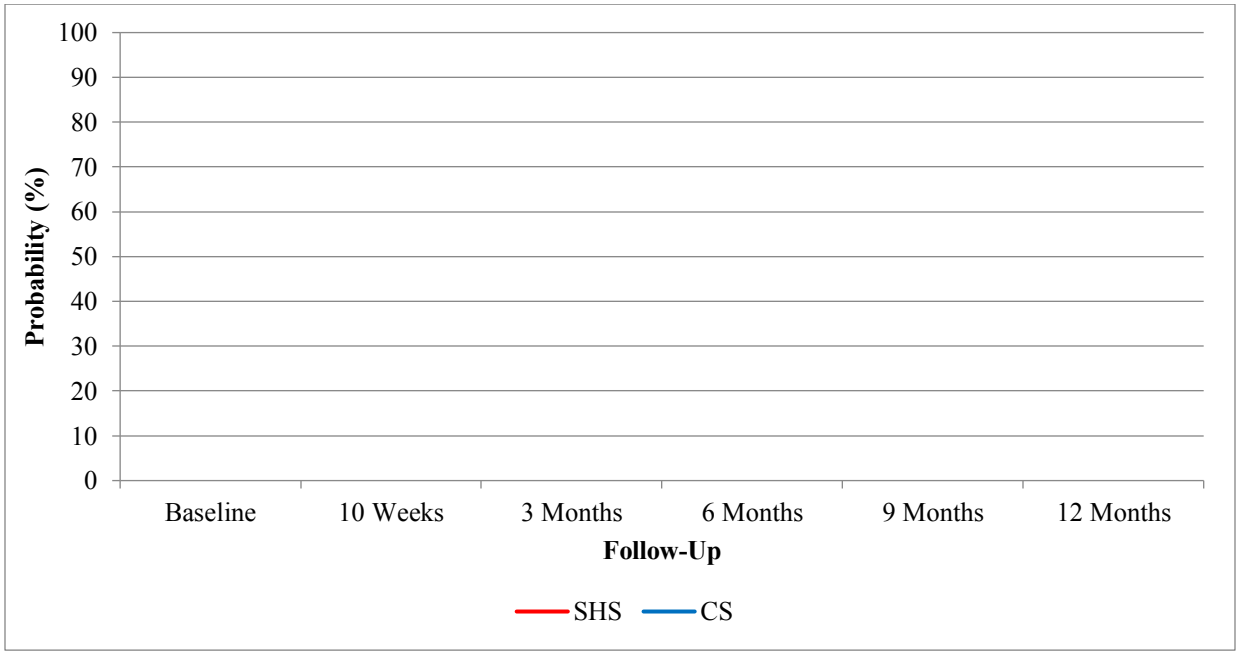


Figure 15: Kaplan-Meier Curves for Radiographic Fracture Healing by Nutritional Supplementation Group (No Significant Interaction Between Implant Type and Supplementation Present)

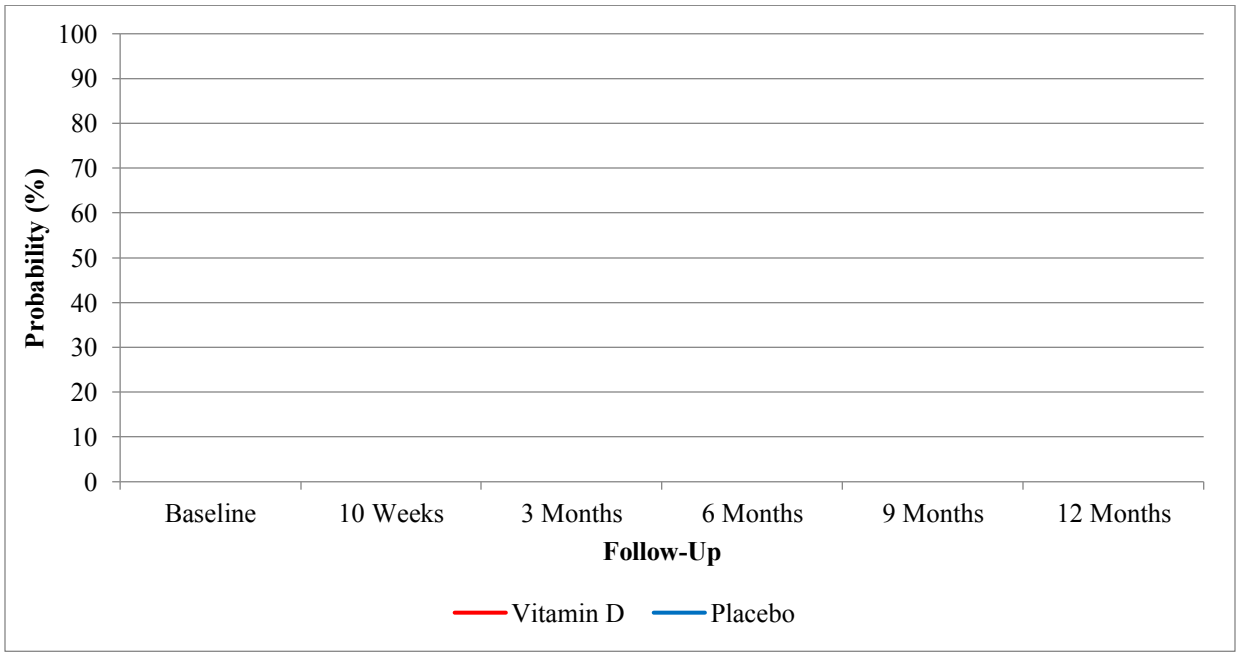


Figure 16: Kaplan-Meier Curves for Radiographic Healing of Ipsilateral Femoral Shaft Fracture (Significant Interaction Between Implant Type and Supplementation Present)

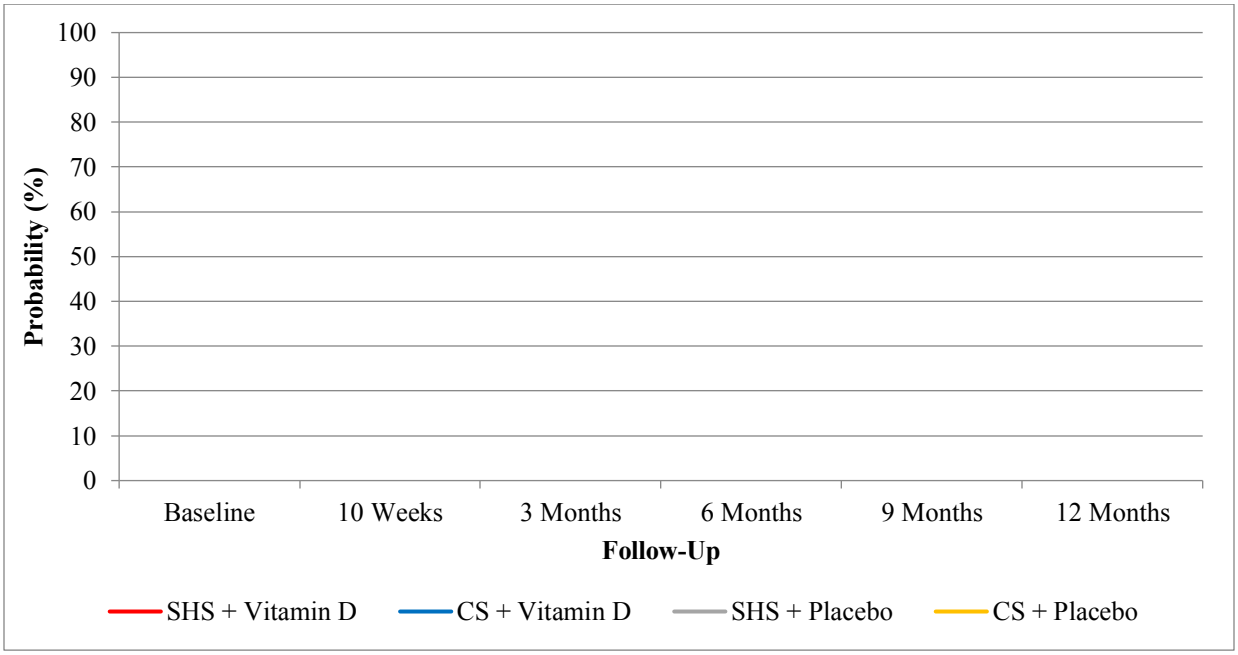


Figure 17: Kaplan-Meier Curves for Radiographic Healing of Ipsilateral Femoral Shaft Fracture by Surgical Treatment Group (No Significant Interaction Between Implant Type and Supplementation Present)

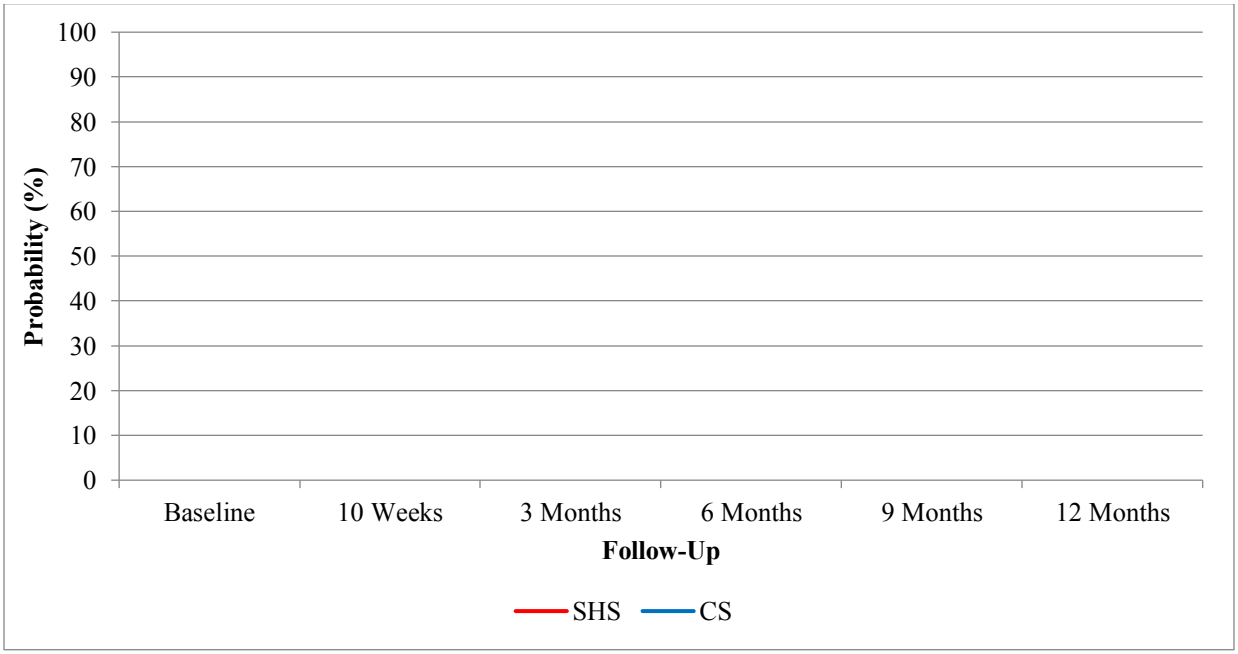
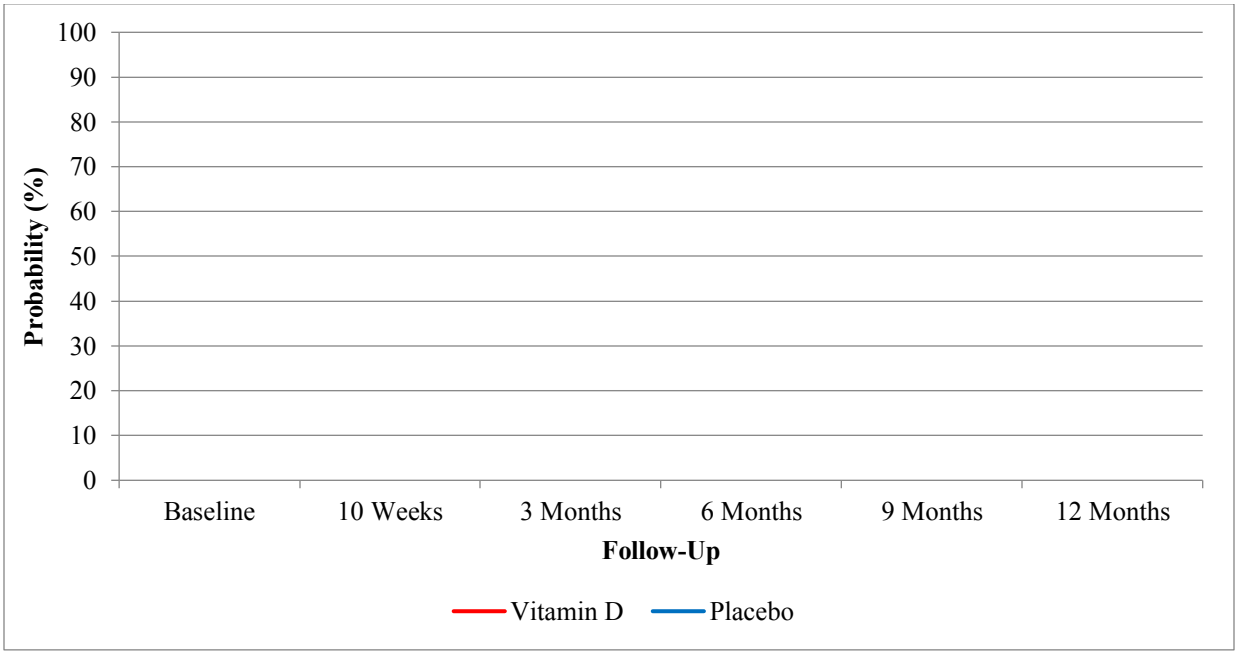


Figure 18: Kaplan-Meier Curves for Radiographic Healing of Ipsilateral Femoral Shaft Fracture by Nutritional Supplementation Group (No Significant Interaction Between Implant Type and Supplementation Present)



9.5 Ipsilateral Femoral Shaft Fractures

For patients with ipsilateral femoral shaft fractures, a time-to-event analysis will be conducted to assess the time to radiographic fracture healing of the ipsilateral femoral shaft fracture (**Tables 21-24**).

Table 21: Secondary Procedures for Ipsilateral Femoral Shaft Fracture and Reasons

Outcome	Definition
Unplanned Secondary Procedures for Ipsilateral Femoral Shaft Fracutre (study event)	Any unplanned surgery related to the treatment of the ipsilateral femoral shaft fracture within 12 months of initial surgery. Specific unplanned secondary procedures include: • Wound closure • Soft tissue procedure • Bone graft • Nail removal • Exchange nailing – retrograde intramedullary nailing • Exchange nailing – antegrade intramedullary nailing • Exchange nailing – Other IF • Nail conversion to plating • Retaining the nail and augmentation with plates • Ilizarov external fixation • Other
Reasons for Secondary Procedures	• Wound healing problem • Compartment syndrome

	• Deep infection • Superficial infection • Shortening • Nonunion • Implant failure/breakage • Prolonged pain at the fracture site • Other

Table 22: Secondary Procedures for Ipsilateral Femoral Shaft Fracture, According to Surgical Treatment (No Significant Interaction Between Implant Type and Supplementation Present)

Secondary Procedure	Variable	Overall N=	Surgical Treatment X N=	Surgical Treatment Y N=	P-Value
Re-operation	Adjudicated Data				
Procedure for Nonunion Bone Graft Nail Removal Exchange nailing – IF Proximal femur osteotomy	Adjudicated Data				

Table 23: Secondary Procedures for Ipsilateral Femoral Shaft Fracture, According to Nutritional Supplementation (No Significant Interaction Between Implant Type and Supplementation Present)

Secondary Procedure	Variable	Overall N=	Nutritional Supplementation X N=	Nutritional Supplementation Y N=	P-Value
Re-operation	Adjudicated Data				
Procedure for Nonunion Bone Graft Nail Removal Exchange nailing – IF Proximal femur osteotomy	Adjudicated Data				

Table 24: Secondary Procedures for Ipsilateral Femoral Shaft Fracture (Significant Interaction Between Implant Type and Supplementation Present)

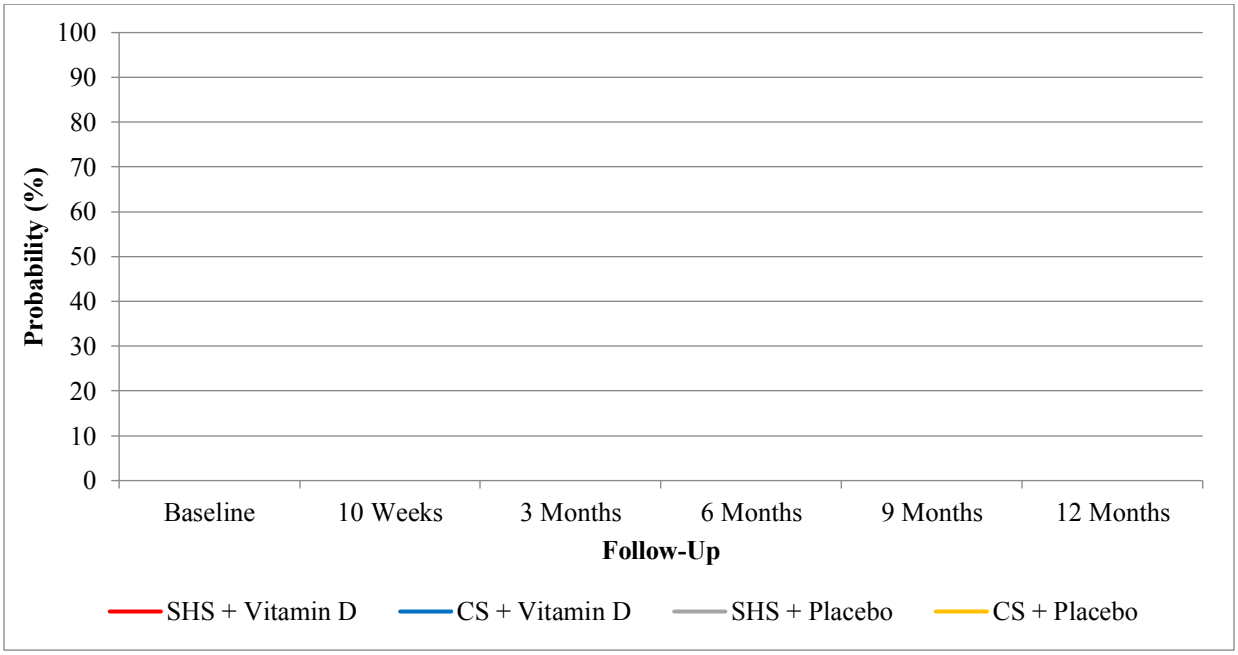
Secondary Procedures	Variable	Overall N=	Surgical Treatment X N=	Surgical Treatment Y N=	Nutritional Supplementation X N=	Nutritional Supplementation Y N=	Hazard Ratio (95% CI)				P-Value
							Surgery X + Supplement X vs. Surgery Y + Supplement X	Surgery X + Supplement Y vs. Surgery Y + Supplement Y	Surgery X + Supplement X vs. Surgery X + Supplement Y	Surgery Y + Supplement X vs. Surgery Y + Supplement Y	
Wound Closure Wound healing problem Compartment syndrome Deep infection Superficial infection Shortening Nonunion Implant failure/ breakage Prolonged pain at the fracture site Other	Adjudicated Data										
Soft Tissue Procedure Wound healing problem Compartment syndrome Deep infection Superficial infection Shortening Nonunion Implant failure/ breakage Prolonged pain at the fracture site Other	Adjudicated Data										
Bone Graft Wound healing problem	Adjudicated Data										

Compartment syndrome Deep infection Superficial infection Shortening Nonunion Implant failure/ breakage Prolonged pain at the fracture site Other											
Nail Removal Wound healing problem Compartment syndrome Deep infection Superficial infection Shortening Nonunion Implant failure/ breakage Prolonged pain at the fracture site Other	Adjudicated Data										
Exchange nailing – Retrograde Intramedullary Nailing Wound healing problem Compartment syndrome Deep infection Superficial infection Shortening Nonunion Implant failure/ breakage Prolonged pain at the fracture site Other	Adjudicated Data										

Exchange Nailing – Antegrade Intramedullary Nailing Wound healing problem Compartment syndrome Deep infection Superficial infection Shortening Nonunion Implant failure/ breakage Prolonged pain at the fracture site Other	Adjudicated Data										
Nail Conversion to Plating Wound healing problem Compartment syndrome Deep infection Superficial infection Shortening Nonunion Implant failure/ breakage Prolonged pain at the fracture site Other	Adjudicated Data										
Retaining the Nail and Augmentation with Plates Wound healing problem Compartment syndrome Deep infection Superficial infection Shortening	Adjudicated Data										

Nonunion Implant failure/ breakage Prolonged pain at the fracture site Other											
Ilizarov External Fixation Wound healing problem Compartment syndrome Deep infection Superficial infection Shortening Nonunion Implant failure/ breakage Prolonged pain at the fracture site Other	Adjudicated Data										
Other Wound healing problem Compartment syndrome Deep infection Superficial infection Shortening Nonunion Implant failure/ breakage Prolonged pain at the fracture site Other	Adjudicated Data										

Figure 19: Kaplan-Meier Curves for Secondary Procedures for Ipsilateral Femoral Shaft Fracture (Significant Interaction Between Implant Type and Supplementation Present)



9.6 Other Follow-Up Data

Characteristic	Variable	Surgical Treatment X N=	Surgical Treatment Y N=	Nutritional Supplementation X N=	Nutritional Supplementation Y N=	Total N=
Patient's Weightbearing Status at Follow-up Visit, n (%) 6 Months Non-Weightbearing Protective Weightbearing or Using Assistive Device Full Weightbearing 12 Months Non-Weightbearing Protective Weightbearing or Using Assistive Device Full Weightbearing	8.2 Q7					
Patient Receiving Physiotherapy or Rehabilitation at Follow-up Visit, n (%) 6 Weeks 3 Months 6 Months 9 Months	8.2 Q8					

Characteristic	Variable	Surgical Treatment X N=	Surgical Treatment Y N=	Nutritional Supplementation X N=	Nutritional Supplementation Y N=	Total N=
12 Months						
Patient Taking Medications at Follow-up Visit, n (%) 6 Months NSAIDS Calcium Steroid Medications 12 Months NSAIDS Calcium Steroid Medications	8.2 Q9					
Secondary Procedures Planned for Patient After 12 Month Follow-up Visit, n (%)	8.4 Q20					

9.7 Adverse Events and Safety Outcomes

An adverse event (AE) is defined as any symptom, sign, illness, or experience that develops or worsens in severity during the study. AEs and safety outcomes will be reported using descriptive statistics including proportions and means with SD (**Table 25**).

Table 25: General Summary of Adverse Events

Characteristic	Variable	Surgical Treatment X N=	Surgical Treatment Y N=	Nutritional Supplementation X N=	Nutritional Supplementation X N=
List of AE, n (%) <Insert most common AE> <Insert 2nd most common AE> <Insert 3rd most common AE>	11.1 Q2				
Serious Adverse Events, n (%)	11.2 Q8				
Time from baseline to AE, mean (SD)	11.1 Q1				
Re-Hospitalized for AE, n (%) Yes No N/A – AE occurred during initial hospitalization N/A – AE occurred while hospitalized for another problem	11.2 Q5				
Treatment, n (%) No Active Treatment Medication(s) Re-operation Other	11.2 Q4				

Related to Surgical Treatment Arm, n (%) Related Probably Related Possibly Related Not Related	11.2 Q6				
Related to Nutritional Supplementation, n (%) Related Probably Related Possibly Related Not Related	11.2 Q7				
Event Unexpected, n (%) Yes No	11.2 Q9				
Outcome, n (%) Not yet resolved Fatal Resolved with no impairment Resolved with mild impairment Resolved with moderate impairment Resolved with severe impairment	11.3 Q11				
Operative Adverse Event Yes	4.2 Q17				

10.0 MISSING DATA

Missing data will be handled using multiple imputation.

11.0 SUBGROUP ANALYSES

Two a priori subgroup analyses are planned using logistic regression models for the primary clinical outcome: 1) the magnitude of treatment effect of the surgical and nutritional supplementation interventions, independently, on undisplaced versus displaced femoral neck fractures and 2) the magnitude of treatment effect of the surgical intervention on emergent (<8 hours) versus non-emergent (≥8 hours) internal fixation (**Tables 26 and 27**). We will use the seven criteria suggested by Oxman and Guyatt to guide inferences about the credibility of our subgroup analyses.[6]

Table 26: Subgroup Analyses Factors, According to Surgical Treatment

Characteristic	Variable	Surgical Treatment X N=	Surgical Treatment Y N=	Total N=
Fracture Displacement, n (%) Undisplaced Displaced	3.3 Q17			

Characteristic	Variable	Surgical Treatment X N=	Surgical Treatment Y N=	Total N=
Time to Internal Fixation, n (%) Emergent (<8 hours) Non-emergent (≥8 hours)	3.3 Q13, 14, 4.1 Q1			

Table 27: Subgroup Analyses Factors, According to Nutritional Supplementation

Characteristic	Variable	Nutritional Supplementation X N=	Nutritional Supplementation Y N=	Total N=
Fracture Displacement, n (%) Undisplaced Displaced	3.3 Q17			
Time to Internal Fixation, n (%) Emergent (<8 hours) Non-emergent (≥8 hours)	3.3 Q13, 14, 4.1 Q1			

12.0 REFERENCES

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