A Blinded Exploratory Randomized Controlled Trial to Determine Optimal Vitamin D_3 Supplementation Strategies for Acute Fracture Healing

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Vita-Shock PROTOCOL

Version: 2.0

Date: 12-Mar-2018

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LIST OF ABBREVIATIONS

Abbreviation	Explanation
AE	Adverse Event
ASBMR	American Society for Bone and Mineral Research
CEO	Center for Evidence-Based Orthopaedics
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CRF	Case Report Form
CTX	C-Terminal Telopeptides of Type I Collagen
FDA	US Food and Drug Administration
FIX-IT	Function IndeX for Trauma
IRB	Institutional Review Board
PACS	Picture Archiving and Communication System
PHI	Personal Health Information
PINP	Amino-Terminal Procollagen Propeptides of Collagen Type I
PTH	Parathyroid Hormone
RCT	Randomized Controlled Trial
REB	Research Ethics Board
RUST	Radiographic Union Score for Tibial fractures
SAE	Serious Adverse Event
SD	Standard Deviation
STC	R Adams Cowley Shock Trauma Center
25(OH)D	25-hydroxy vitamin D

STUDY SUMMARY

Methodology	Phase II exploratory randomized controlled trial (RCT)
Coordinating Center	Center for Evidence-Based Orthopaedics (CEO), McMaster University, Hamilton, ON
Clinical Site	R Adams Cowley Shock Trauma Center (STC), Baltimore, MD
Primary Aim	The primary objective is to determine the effect of vitamin D_3 supplementation on fracture healing at 3 months.
Secondary Aim	The secondary objective is to determine if 25-hydroxy vitamin D [25(OH)D] serum levels are associated with fracture healing at 3 months.
Other Secondary Objective	The other secondary objective is to confirm study protocol feasibility for a larger definitive phase III efficacy RCT to determine the optimal vitamin D_3 dosing regimen to reduce re-operations for fracture healing complications in healthy adult patients.
Diagnosis and Main Inclusion Criteria	Healthy adults ages 18-50 years with non-osteoporotic femoral or tibial shaft fractures who are treated with intramedullary fixation will be enrolled. Only acute fractures will be eligible.
Treatment Groups and Study Products	Each participant will be randomized to 1 of 4 treatment groups: 1) 150,000 IU loading dose vitamin D_3 plus daily dose placebo; 2) loading dose placebo plus 4,000 IU vitamin D_3 per day; 3) loading dose placebo plus 600 IU vitamin D_3 per day; or 4) loading dose placebo plus daily dose placebo. All doses of vitamin D_3 supplements/placebo will be provided in a blinded manner. The daily treatment will commence within 1 week of injury and will be taken for 3 months. The loading dose vitamin D_3 supplements/placebo will be given within 1 week of injury and at 6 weeks post-injury. All doses of vitamin D_3 and the placebo will be obtained from Bio-Tech Pharmacal, Inc. (Fayetteville, AK).
Length of Follow-Up	The primary outcome will be assessed at 3 months post-fracture. Participants will be followed for 12 months.

Study Outcomes	Fracture healing (primary outcome) will be assessed as follows: 1) clinical fracture healing will be measured using the Function IndeX for Trauma (FIX-IT), 2) radiographic fracture healing will be measured using the Radiographic Union Score for Tibial fractures (RUST), and 3) biological fracture healing will be measured using serum levels of cross-linked C-terminal telopeptides of type I collagen (CTX) and amino-terminal procollagen propeptides of collagen type I (PINP). The secondary outcome will be assessed by measuring 25(OH)D serum levels. Correlations will be assessed between participants' 25(OH)D levels at enrolment, changes in 25(OH)D levels from enrolment to 3 months, and 25(OH)D levels at 3 months and fracture healing as described above. The other secondary outcomes will include assessing supplementation adherence between daily and loading doses, confirming participant safety as measured by adverse events (AEs) and serum levels of calcium and parathyroid hormone (PTH), and assessing protocol adherence (e.g. completion of outcome assessment and participant follow-up).
Sample Size	96 patients will be included.

1.0 INTRODUCTION

Vitamin D supplements are increasingly being recommended to healthy adult fracture patients without an osteoporotic injury.[1] Although this is a relatively new practice pattern, the basis for this adjunct therapy is grounded in the high hypovitaminosis D prevalence rates (up to 75%) among healthy adult fracture patients,[1] and the strong biologic rationale for the role of vitamin D in fracture healing.[2–6] Briefly, experimental animal studies have demonstrated that the concentration of vitamin D metabolites is higher at a fracture callus compared to the uninjured contralateral bone,[3–5] vitamin D supplementation leads to decreased time to union and increased callus vascularity,[2] and increases mechanical bone strength compared to controls.[6] While evidence to confirm that vitamin D supplementation improves fracture healing in clinical studies does not exist, the pre-clinical data are compelling and worthy of further investigation.

With modern orthopaedic surgical care, rates of complications following tibia and femoral shaft fractures can be as high as 15%. Complications, including delayed union, nonunion, or infection often require secondary surgical procedures[7–9] and result in profound personal and societal economic costs.[10–12] While surgeons continue to seek advances in surgical technique, it is becoming increasingly obvious that innovations in orthopaedic techniques or implants are unlikely to eliminate complications.[13] As a result, considerable attention is currently focused on adjunct biologic therapies, such as vitamin D.[14–16]

A recent survey of 397 orthopaedic surgeons showed that only 26% routinely prescribe vitamin D supplementation to adult fracture patients.[17] Of the 93 surgeons who indicated that they routinely prescribe vitamin D supplementation, 29 different dosing regimens were described ranging from low daily doses of 400 IU to loading doses of 600,000 IU.[17] This suggests a high level of clinical uncertainty surrounding the use and optimal dose of vitamin D supplementation in adult fracture patients. If vitamin D supplementation improves fracture healing outcomes, then there is a large opportunity to increase its use; however, before widespread adoption occurs, research is needed to optimize the dosing strategy, establish the dosing safety in the immobilized fracture healing population, and overcome potential medication adherence issues among the often-marginalized patients that suffer trauma.

The long-term goal of our research program is to conduct a large phase III RCT to determine which dose of vitamin D_3 supplementation optimally improves acute fracture healing outcomes in healthy adult patients (18-50 years). The current proposed phase II exploratory trial will perform important preliminary work to test the central hypothesis that vitamin D_3 dose and timing of administration is critical for improving fracture healing at 3 months. This trial will also inform the feasibility of the large phase III RCT. This trial is registered at clinicaltrials.gov (Identifier number: NCT02786498).

2.0 STUDY AIMS AND OBJECTIVES

2.1 Primary Aim

The primary aim is to assess the effect of vitamin D_3 supplementation on fracture healing at 3 months. Fracture healing will be assessed as follows: 1) clinical fracture healing will be measured using the Function IndeX for Trauma (FIX-IT),[18] 2) radiographic fracture healing will be measured using the Radiographic Union Score for Tibial fractures (RUST),[19–22] and 3) biological fracture healing will be measured using serum levels of cross-linked C-terminal telopeptides of type I collagen (CTX) and amino-terminal procollagen propeptides of collagen type I (PINP).[23]

2.2 Secondary Aim

The secondary aim is to determine if 25(OH)D serum levels are associated with fracture healing at 3 months.

2.3 Other Secondary Objective

The other secondary objective is to confirm study protocol feasibility for a larger definitive phase III efficacy RCT to determine the optimal vitamin D_3 dosing regimen to reduce re-operations for fracture healing complications in healthy adult patients.

2.4 Hypotheses for the Primary and Secondary Objectives

Primary Objective: Lower extremity shaft fractures heal via callus formation and secondary bone healing. This seminal process begins within a few weeks of injury and vitamin D metabolites have been extensively implicated in this stage of healing. During these early weeks, circulating vitamin D levels are most likely to be critical to bone healing; therefore, we hypothesize:

1) *High doses (loading or daily) will increase healing compared to low daily dose*. Using high doses will rapidly increase the circulating vitamin D available during fracture callus formation.
2) *High loading dose increases healing compared to high daily dose.* Loading doses will overcome medication adherence issues and increase circulating vitamin D even more rapidly than daily doses.
3) *Low daily dose will increase healing compared to placebo*. While the low daily dose is not expected to increase circulating vitamin D as rapidly as the high dose strategies, this comparison will determine if rapid serum increases are necessary to improve fracture healing.

Secondary Objective: Based on experimental data and the role of vitamin D on bone metabolism, a correlation between circulating vitamin D levels and fracture healing is expected; however, the efficacy of various supplementation strategies may be dependent on the patient's baseline vitamin D status or other related changes. For example, it is known that the dose response of supplementation varies depending on the patient's serum 25(OH)D levels, with larger increases seen in patients with serum levels <20ng/ml.

3.0 METHODS

3.1 Study Setting
This study will be coordinated jointly by the University of Maryland, R Adams Cowley Shock Trauma Center (STC), Baltimore, MD and McMaster University, Center for Evidence-Based Orthopaedics (CEO), Hamilton, ON. Patients will be enrolled from the STC. The CEO will be responsible for the protocol, data management, and data analysis.

3.2 Eligibility Criteria
The inclusion criteria are: 1) adult men or women ages 18-50 years; 2) closed or low grade open (Gustilo type I or II) tibial or femoral shaft fracture;[24] 3) fracture treated with a reamed, locked, intramedullary nail; 4) acute fracture (enrolled within 7 days of injury); and 5) provision of informed consent. Fifty years was selected as the upper age limit to minimize potential confounding with post-menopausal endocrine changes that affect bone metabolism. For the purposes of the study, femoral shaft fractures will be defined as any injury in which the majority of fracture line is distal to the lesser trochanter and proximal to the distal metaphyseal flare of the femoral condyles (**Figure 1**). Intertochanteric extension or distal articular extension is permitted. Similarly, a tibial shaft fracture will be defined as an injury with a primary fracture line between the proximal meta-diaphyseal flare to the distal metaphyseal region ending one joint width proximal to the tibial plafond (**Figure 2**). Intra-articular extension is permitted.

The exclusion criteria are: 1) osteoporosis; 2) stress fractures; 3) elevated serum calcium (>10.5 mg/dL); 4) atypical femur fractures as defined by American Society for Bone and Mineral Research (ASBMR) criteria;[25] 5) pathological fractures secondary to neoplasm or other bone lesion; 6) patients with known or likely undiagnosed disorders of bone metabolism such as Paget's disease, osteomalacia, osteopetrosis, osteogenesis imperfecta etc.; 7) patients with hyperhomocysteinemia; 8) patients with an allergy to vitamin D or another contraindication to being prescribed vitamin D; 9) patients currently taking an over the counter multivitamin that contains vitamin D and are unable or unwilling to discontinue its use for this study; 10) patients who will likely have problems, in the judgment of the investigators, with maintaining follow-up; 11) pregnancy; 12) patients who are incarcerated; 13) patients who are not expected to survive their injuries; and 14) other lower extremity injuries that prevent bilateral full weight-bearing by 6 weeks post-fracture.

Patients with multiple injuries or multiple tibial and femoral shaft fractures will be eligible for inclusion; however, only the most severe eligible fracture will be included (as determined by the treating surgeon using the grade of soft tissue injury using the Tscherne classification system for closed fractures[26] and the Gustilo classification system for open fractures).[24]

3.3 Recruitment Strategy and Patient Screening
All patients presenting to participating surgeons between the ages of 18 to 50 years with a tibial or femoral shaft fracture will be screened. Potentially eligible patients will be approached to participate in the trial. All screened patients will be classified as included or excluded.

3.4 Randomization Methods

Each participant will be randomized to 1 of 4 treatment groups: 1) 150,000 IU loading dose vitamin D_3 plus daily dose placebo; 2) loading dose placebo plus 4,000 IU vitamin D_3 per day; 3) loading dose placebo plus 600 IU vitamin D_3 per day; or 4) loading dose placebo plus daily dose placebo. The daily vitamin D_3 supplements/placebo will be provided in a blinded manner. The daily treatment will commence within 1 week of injury and will be taken for 3 months. The loading dose vitamin D_3 supplements/placebo will be given within 1 week of injury and at 6 weeks (+/- 2 weeks) post-injury.

Allocation to the 4 study groups 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: fracture type (closed vs. open) and long bone fracture (tibia vs. femur).

3.5 Vitamin D_3 (Cholecalciferol) Treatment Groups

3.5.1 Blinded administration

The loading dose of 150,000 IU will consist of 3 50,000 IU capsules of vitamin D_3. The loading dose placebo will consist of 3 capsules that are identical to the 50,000 IU capsules with no active ingredient. The loading dose vitamin D_3 supplements/placebo will be given within 1 week of injury and at 6 weeks (+/- 2weeks) post-injury while in hospital or at the outpatient fracture clinic.

The daily vitamin D_3 supplements/placebo will be provided in a blinded manner and the daily treatment will commence within 1 week of injury. The daily doses (4,000 IU, 600 IU, and placebo) will be identical and will be comprised of one capsule. Patients will be given a bottle of either active vitamin D_3 or placebo capsules and will be instructed to take one capsule daily for 3 months. The placebo capsules will have no active ingredients and will be identical to the vitamin D capsules. To measure supplementation adherence, participants will be asked to bring their bottles to their follow-up visits. At the 3-month visit, participants will return their bottle to the clinical research coordinator. If the participant does not return the bottle, the clinical research coordinator will provide them with an envelope to return it via mail.

All doses of vitamin D and placebo will be obtained from Bio-Tech Pharmacal, Inc. (Fayetteville, AK). The unblinding protocol can be found in **Figure 3**. Following the completion of the study, participants may be unblinded their treatment group upon request.

3.5.2 Vitamin D_3 dose rationale

The doses selected are based on biologic rationale, current practice patterns, and existing guidelines. The goal of the high dose arms is to rapidly increase circulating vitamin D and serum 25(OH)D during the early callus fracture healing periods. Conversely, while the low daily dose is not expected to increase circulating vitamin D as quickly as the high dose strategies, this treatment arm will determine if rapid serum increases are necessary to improve fracture healing. Finally, the placebo control arm is needed to demonstrate the

relative efficacy of each treatment arm and is also necessary to represent current practice at most trauma centers in North America.

- High loading dose: 150,000 IU D_3 loading doses can be administered easily with three 50,000 IU D_3 pills. We expect this dose to increase circulating vitamin D levels the fastest. While we acknowledge that many non-orthopaedic clinicians may prefer more frequent large doses, such as 50,000 IU weekly, our loading dose strategy has been chosen to correspond with the standard post-operative clinical follow-up schedule. This is important for generalizability and is likely to overcome potential supplementation adherence issues within the adult fracture population that is often predominantly lower socioeconomic patients. This high loading dose is also in the mid-range of other previous large loading doses used safely in fracture patients and is similar to the total cumulative 3-month dose of our high daily dose group.
- High daily dose: 4,000 IU D_3 represents an alternative high dose strategy and it corresponds to the tolerable upper daily intake level suggested by the Institute of Medicine (IOM).[27] While this is the IOM's upper limit, the Endocrine Society has recommended adults can safely take up to 10,000 IU per day,[28] further suggesting that our 4,000 IU dose should be well-tolerated.
- Low daily dose: 600 IU D_3 is a common dose and approved indication for maintaining general bone health. 600 IU is also the IOM's Recommended Dietary Allowance for all individuals ages 1-70 years.[27] This represents our most conservative supplementation strategy, but its use is common among surgeons prescribing vitamin D and previous studies have shown its efficacy for increasing serum 25(OH)D levels.
- Placebo: Finally, we are including a placebo group because it is important to include placebo-controlled comparisons to our active supplements during this exploratory phase of research. Not only does placebo reflect our usual clinical practice of no supplementation, this Phase II comparison will define our rationale and selection of the control group for the definitive trial. If there are no preliminary efficacy differences between low dose supplementation and placebo, then the low dose supplement could be used as the control group in the Phase III trial. This would obviate potential criticisms for performing a Phase III placebo-controlled trial in a population with a high prevalence of hypovitaminosis D. Given the small number of patients receiving placebo (n=24), the Phase II screening design of this trial, and the fact that receiving placebo does not represent an increased risk of study participation since it is our standard clinical practice, we do not believe this poses an ethical concern. We have used a similar rationale to explain the placebo blinding in the FAITH-2 pilot trial and this has been accepted at over 20 research ethics boards, with no clinical site disallowing the protocol.

3.5.3 Storage and administration

As per the standard operating procedures at the STC, the study supplements/placebo will be stored at room temperature in accordance with the manufacturer's recommendations. The research personnel will maintain an inventory and temperature log to ensure the integrity of the supplements. Study supplementation will begin within 1 week of injury, and it is expected that the research personnel will provide the supplementation to the participant upon discharge from the hospital. Therefore, the hospital pharmacy will not be used to administer this out-patient, over-the-counter medication. The research personnel

have previous experience administering vitamin D supplements/placebo to study patients at the recruiting hospital, the STC.

3.5.4 Potential adverse events associated with vitamin D

A recent systematic review comprehensively examined the effectiveness and safety of vitamin D supplementation among all ages of adult fracture patients.[27] The majority of research has been performed in elderly fracture populations; however, the safety of a wide range of doses is well established. Studies with doses of 4,000 IU daily and loading doses from 50,000 IU for up to 7 days or single loading doses up to 500,000 IU have been used without complication.[29]

Since vitamin D regulates PTH and serum calcium levels, it is theoretically possible that vitamin D supplementation could lead to hypercalcemia. Of the 1,088 patients included in the systematic review, 4 cases of hypercalcemia were reported (0.4%).[30] Furthermore, there have been no cases of hypercalcemia in several high loading dose clinical trials. Regardless, we will monitor serum calcium levels at enrolment, 6 weeks, and 3 months post-fracture, and clinical signs of hypercalcemia will be sought at all clinical encounters. If hypercalcemia is identified, participants will be instructed to stop their vitamin D supplementation immediately and the hypercalcemia will be treated as indicated.

Finally, we will monitor for increased falls among the study participants. While we do not expect to observe this adverse event (AE) in our 18 to 50 year-old adult population, a recent study of 200 elderly fracture patients found that a 60,000 IU monthly loading dose and 24,000 IU monthly loading dose plus 300 µg of calcifediol were associated with increased falls compared to the control group.[31] This single study contradicts several other high loading dose clinical trials, and these concerns have not been borne out of the healthy adult fracture population. This may be a result of the fact that supplementation in the non-osteoporotic fracture population has not been extensively studied (highlighting the need for the proposed research), or because these concerns regarding the risk of falls do not apply to healthy adults without osteoporosis.

3.5.5 Concomitant calcium supplementation

In addition, although calcium supplementation is often recommended concomitantly with vitamin D for osteoporosis prevention, for our non-osteoporotic study population the necessity of calcium supplementation is controversial and will not be provided because of the increased risk of kidney stones, hypercalcemia, and potential confounding. This rationale has also been outlined by other researchers performing RCTs involving vitamin D supplementation.

3.6 Surgical Technique and Post-Operative Rehabilitation

3.6.1 Surgical technique

The study protocol will not dictate the surgical technique. Based on the study's eligibility criteria, all participants must receive a reamed, locked, intramedullary nail for their tibial or femoral shaft fracture. The number and orientation of locking screws is at the discretion of the treating surgeon, as there have been no studies that demonstrate clinical superiority

of any locking screw strategy. Any concomitant fracture lines that extend into the adjacent articular areas may be treated with additional fixation as indicated.

3.6.2 Post-operative rehabilitation

Full weight-bearing as tolerated is recommended for all isolated tibial and femoral shaft fractures. In the presence of additional lower extremity fractures, intra-articular extension, or other concomitant soft tissue injuries, participants may be restricted to protected weight-bearing (partial or no weight) for up to 6 weeks post-fracture. If additional contralateral injuries are present, both limbs must be eligible for full weight-bearing by 6 weeks post-fracture.

3.7 Primary and Secondary Outcome Measures

3.7.1 Primary outcome

Fracture healing will be assessed as follows: 1) clinical fracture healing will be measured using FIX-IT, 2) radiographic fracture healing will be measured using the RUST, and 3) biological fracture healing will be measured using serum levels of CTX and PINP.

Clinical Healing: FIX-IT is a standardized measure of weight-bearing and pain in patients with lower extremity fractures, specifically tibia and femur fractures.[18] Preliminary validation of the FIX-IT has demonstrated high inter-rater agreement and moderate correlation with the physical scores of the Short Form-36.[18] It has been used in other studies to assess clinical fracture healing.

Radiographic Healing: The RUST score assesses the presence of bridging callus or a persistent fracture line on each of 4 cortices.[19–22] This score has been previously validated and found to have greater inter-rater reliability when compared with surgeons' general impression of the cortical bridging.[19–22] RUST has been widely used to assess radiographic fracture healing.[19–22] An orthopaedic surgeon who is independent of the study will review the images and assign a RUST score.

Biological Healing: CTX is a bone-resorption marker and previous research has found that it rises 1 week after fracture of the tibial shaft and remains elevated throughout fracture healing.[23] PINP is a bone-formation marker and prior research has found that it is highest at 12 weeks after fractures of the tibial shaft and proximal femur.[32]

The primary time point for assessing fracture healing will be at 3 months post-injury. This time point was selected because it coincides within the standard clinical follow-up schedule, and because it has the greatest potential to detect differences in short-term fracture healing. While we expect the 1-year fracture union rate to be approximately 95% for the femur fractures[32] and 75% for the tibia fractures (unpublished data from the SPRINT trial),[7] improved early fracture healing is biologically plausible. The median time to fracture union for tibia fractures is 4 months; therefore, many patients are still experiencing morbidity from their injury at the 3-month visit and decreasing the time to union would be an important patient benefit.

3.7.2 Secondary outcome

The secondary outcome will be assessed by measuring 25(OH)D serum levels. Correlations will be assessed between participants' 25(OH)D levels at enrolment, changes in 25(OH)D levels from enrolment to 3 months, and 25(OH)D levels at 3 months and fracture healing as described above.

3.7.3 Other secondary outcomes

The other secondary outcomes will include assessing supplementation adherence between daily and loading doses, confirming participant safety as measured by AEs and serum levels of calcium and parathyroid hormone (PTH), and assessing protocol adherence (e.g. completion of outcome assessment and participant follow-up).

Adherence with vitamin D supplementation will be assessed by participant self-report, by counting the tablets for the daily doses at each follow-up, and by direct observation for the loading doses.

Participant safety will be assessed by AEs, defined as any symptom, sign, illness, or experience that develops or worsens in severity during the course of this study. Within the AEs collected, fracture healing complications will be identified, and will include nonunion (defined as failure of the fracture to progress towards healing for 2 consecutive months and at least 6 months post-fracture), delayed union (defined as a failure of progression of fracture healing beyond the expected median healing time of 4 months with pain at the fracture site), hardware failure (defined as broken or bent nail or locking screw),[33] wound healing problems (previously published criteria by Anglen 2005), and infection (superficial and deep as defined by Centers for Disease Control and Prevention (CDC) criteria). Wound healing problems and infection are a part of the composite fracture healing complication outcome because previous animal and infectious disease clinical research has suggested that vitamin D can improve wound healing and reduce infections.[34–37] In addition to AEs, serum levels of calcium and PTH will be monitored and we will record results of the participants' pre-operative metabolic profile. These data will be used to understand the baseline metabolic health of the participants and will be used as needed in the event of suspected AEs.

Participant adherence with the protocol will be assessed by monitoring the completion of outcome measures, including clinic assessments (FIX-IT), radiographs (RUST), and blood work (CTX, PINP, 25(OH)D, calcium, and PTH), documentation of AEs and re-operations, and completion of follow-up to 12 months.

3.7.4 Data collection and participant follow-up

Upon providing informed consent, baseline demographics will be collected from the patient and from their medical chart (**Table 1**). This includes demographic, medical history, pre-operative blood work-up details (e.g. kidney and liver function tests, calcium, phosphate, and albumin), injury details, fracture characteristics, details on the surgical management of their fracture, and rehabilitation details. Participants will have blood drawn within the fracture clinic that will be analyzed for calcium levels and for CTX, PINP, 25(OH)D, and

PTH (See Section 3.7.5). Post-operative x-rays will be taken as per standard of care (See Section 3.7.6).

Participants will be followed at standard clinical visit intervals for 12 months post-injury including 6 weeks, 3 months, 6 months, 9 months, and 12 months. The Schedule of Events (**Table 1**) details the requirements and procedures for each visit. Participants will have blood drawn within the fracture clinic that will be analyzed for calcium, CTX, PINP, 25(OH)D, and PTH serum levels at 6 weeks and 3 months (See Section 3.7.5). Post-operative x-rays will be taken as per standard of care at each follow-up visit (See Section 3.7.6). Participants will be assessed clinically for FIX-IT at each visit. All study outcomes (as defined above) will be documented on the case report forms (CRFs) at each follow-up visit. A 12-month follow-up was selected because is a standard follow-up period for patients with tibial and femoral shaft fractures and it is a commonly used follow-up period for similar fracture trials.[7,38] In addition, it is a commonly referenced time period for fracture healing complications requiring reoperation, and will further inform decisions surrounding the larger, definitive phase III RCT.

3.7.5 Analysis of blood samples

Serum calcium testing will be performed by the hospital laboratory and will be part of the unblinded medical chart for patient safety. The remainder of serum samples (PTH, 25(OH)D, PINP, CTX) will be analyzed in a blinded manner at the end of the study. Laboratory personnel at the University of Maryland's Muscle Research Laboratory will process the samples for storage in the -80° C freezer. Upon completion of all blood work for the study, the serum samples will be transferred to the Institute for Clinical and Translational Research Clinical Research Unit Core Laboratory to be analyzed as a single batch to eliminate inter-batch assay variability. The results of the analyses will be sent to the CEO to be added to the REDCap study database and included within the final data analysis. The treating surgeon will remain blinded to these results. Participants may request the results of their blood analysis at the end of the study.

3.7.6 Analysis of radiographs

The radiographs will be stored in the STC Picture Archiving and Communication System (PACS) at the STC and then sent to the CEO for the review of radiographic fracture healing (RUST) by an independent practicing orthopaedic surgeon.

3.8 Participant Retention

Once a participant is enrolled in the trial, every reasonable effort will be made 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.[7,38–40] 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 4)**.[41]

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 supplements, 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).

4.0 STATISTICAL PLAN

4.1 Sample Size Determination

This trial will use a phase II randomized screening design to facilitate non-definitive comparisons of three vitamin D_3 dosing regimens. Using the principles outlined by Rubinstein et al, the statistical parameters have been carefully chosen to ensure a reasonable sample size and meaningful results.[42] Consistent with previous recommendations, an α and β of 0.20 was chosen with a target mean difference of 17-20%, depending on the fracture healing measure. There will be no adjustments for multiple testing given the exploratory nature of the study design.

Based on the original instrument development and validation in tibia and femur fracture patients, it is expected that the low dose and control groups will have a mean 3-month FIX-IT score of 8 (standard deviation (SD) 3).[18] Assuming the high dose groups will achieve a mean 2 point increase (17% mean difference), 21 patients are required in each group. The same sample size requirements will be applied for comparisons using the RUST instrument based on similar assumptions and recent literature (2 point mean difference, 8 vs. 6, SD 3).[19–22] Clinically important changes in the PINP and CTX markers are unknown; however, in a previous study of tibia fracture healing, Veitch et al observed concentrations of both bone turnover markers approximately 100% greater than baseline values.[43] Given the large changes observed in these bone turnover markers, the same criteria will be applied for identifying a potentially clinically beneficial regimen and remain powered to detect a mean difference of 20% (SD 30%). Finally, the sample size will be increased to account for a 10% loss to follow-up, for a total enrolment of 24 patients per allocation group (96 total).

4.2 Statistical Methods

All outcome analyses will be exploratory and adhere to the intention-to-treat principle. As treated sensitivity analyses will also be conducted.

4.2.1 Specific Aim

Each measure of fracture healing will be described with its mean and SD. For our primary analysis, comparisons for the 3 hypotheses (Section 2.4) will be made using an independent t-test and significance set at α=0.20 (**Table 2**). Hypothesis 1 compares high dose supplementation versus low dose. To test this hypothesis, we will combine the two high dose groups (loading and daily) for a 2:1 comparison against the low daily dose group. All other comparisons will be 1:1 based on the treatment groups outlined.

4.2.2 Secondary Aim

To test the hypotheses of the Secondary Aim, univariate analyses will be used to explore associations between 3-month fracture healing and 3 assessments of serum 25(OH)D

levels: enrolment, 3 months, and change in levels between enrolment and 3 months. Significance will be set at α=0.20. Additional descriptive analyses will be performed for serum 25(OH)D at each time point (**Table 3**).

4.2.3 Other Secondary Outcomes

All other secondary outcomes will be presented using point estimates and appropriate measures of variance to describe supplementation adherence, participant safety, and key aspects of participant compliance with the protocol (**Table 4**). Supplement adherence will be summarized using means and 95% confidence intervals for participant self-reporting and the mean cumulative dose taken at 3 months. The incidence of AEs and re-operations for fracture healing complications in each group will be described with counts and proportions. Serum levels of calcium and PTH will be summarized using means and 95% CIs. Participant compliance with the protocol will be summarized descriptively with counts and proportions.

4.2.4 As Treated Sensitivity Analyses

The specific aim and the relevant other secondary outcome analyses will be repeated following as-treated analyses. These sensitivity analyses will be completed after the above outcome analyses have been completed and once unblinding has occurred. As treated will be defined as participants who received both loading doses of vitamin D and participants who did not miss 20 or more daily doses of vitamin D. Therefore, participants who missed a loading dose of vitamin D and participants who missed 20 or more daily doses of vitamin D will not be included in the as-treated sensitivity analyses.

5.0 DATA MANAGEMENT

The CRFs will be the primary data collection tool for the study. All data requested on the CRF must be recorded. All data will be entered into a REDCap study database (McMaster University) and double verified.

6.0 ETHICS AND DISSEMINATION

6.1 Research Ethics Approval

This protocol will be reviewed and approved by the University of Maryland Institutional Review Board (IRB) and the McMaster University Research Ethics Board (REB) prior to commencement of the study.

6.2 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.
- Discuss the study with the potential participant and answer any questions he or she asks.

- Allow the potential participant an opportunity to discuss participation with their family, friends, or family physician if desired.
- Confirm that the participant 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.

6.3 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.
- 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 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 who 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.

6.4 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 the University of Maryland IRB and the McMaster University REB. 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.

6.5 Adverse Event Reporting and Definitions

6.5.1 Adverse event

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

6.5.2 Serious adverse event

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

- Fatal
- Life threatening
- Requires or prolongs hospital stay

- Results in persistent or significant disability or incapacity
- A congenital anomaly or birth defect
- An important medical event

All SAEs must be recorded and promptly submitted to the local IRB.

6.5.3 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 local IRB.

6.5.4 Adverse drug reactions

An adverse drug reaction is an injury caused by taking a medication. All adverse drug reactions that are considered both serious and unexpected are to be reported to the US Food and Drug Administration (FDA) within the following time periods of the information becoming available: 1) within 7 days for events that are fatal or life-threatening and 2) within 15 days for all other events that are not fatal or life-threatening.

6.6 Dissemination Policy

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

Table 1: Schedule of Events

Assessment	Visit 1: Screening & Baseline	Visit 2: 6 Weeks	Visit 3: 3 Months	Visit 4: 6 Months	Visit 5: 9 Months	Visit 6: 12 Months
Screening	●					
Serum Calcium Analysis	●*	●	●			
Informed Consent	●					
Randomization	●					
Collection of Baseline Data (Demographic, Serum Metabolic Panel, Fracture, & Surgical Data)	●					
Nutritional/Placebo Supplementation**	●	●	●			
Assessment of Clinical Fracture Healing (FIX-IT)		●	●	●	●	●
X-Rays of Tibia or Femur	●	●	●	●	●	●
Assessment of Radiographic Fracture Healing (RUST)		●	●	●	●	●
Serum Bone Marker Analysis (CTX & PINP)	●	●	●			
Assessment of Adherence to Supplementation		●	●			
Laboratory Serum 25(OH)D Analysis	●	●	●			
Assessment for AEs		●	●	●	●	●
Serum PTH Level Analysis	●	●	●			
Assessment of Fracture Healing Complications		●	●	●	●	●

*To be assessed as eligibility criteria
**Must occur within 1 week of fracture

Table 2: Primary Outcome Analysis

Objective	Hypothesis	Fracture Healing Outcome	Method of Analysis
To determine the effect of vitamin D_3 dose on fracture healing at 3 months	*High doses of supplementation (loading or daily) will increase healing compared to low daily dose*. Using high doses will rapidly increase the circulating vitamin D available during fracture callus formation.	1. FIXIT (Clinical) 2. RUST (Radiographic) 3. PINP (Biologic) 4. CTX (Biologic)	Patients in the high loading dose & high daily dose groups will be combined for a 2:1 comparison against low daily dose group using an *Independent t-test* (alpha=0.20)*
To determine the effect of vitamin D_3 frequency on fracture healing at 3 months	*High loading dose increases healing compared to high daily dose.* Loading doses will overcome medication adherence issues and increase circulating vitamin D even more rapidly than daily doses.	1. FIXIT (Clinical) 2. RUST (Radiographic) 3. PINP (Biologic) 4. CTX (Biologic)	Comparisons between the high loading dose & high daily dose groups will be made using an *Independent t-test* (alpha=0.20)*
To determine the effect of low amounts of vitamin D_3 supplementation on fracture healing at 3 months	*Low daily dose will increase healing compared to placebo*. While the low daily dose is not expected to increase circulating vitamin D as rapidly as the high dose strategies, this comparison will determine if rapid serum increases are necessary to improve fracture healing.	1. FIXIT (Clinical) 2. RUST (Radiographic) 3. PINP (Biologic) 4. CTX (Biologic)	Comparisons between the low daily dose & placebo groups will be made using an *Independent t-test* (alpha=0.20)*

**Using Phase II screening trial approach, comparisons are non-definitive and an increased alpha level has been adopted.*

Table 3: Secondary Outcome Analysis

Objective	Hypothesis	Fracture Healing Outcome	Method of Analysis
To determine if 25(OH)D serum levels are associated with fracture healing at 3 months	There will be an association between fracture healing and: 1) patients' enrolment serum 25(OH)D, 2) their change in 25(OH)D from enrolment to 3 months, 3) their 25(OH)D level at 3 months	1. FIXIT (Clinical) 2. RUST (Radiographic) 3. PINP (Biologic) 4. CTX (Biologic)	Associations will be quantified using *Univariate Analysis* (alpha=0.20)*.

**Using Phase II screening trial approach, comparisons are non-definitive and an increased alpha level has been adopted.*

Table 4: Other Secondary Outcomes Analysis

Objective	Hypothesis	Outcome	Method of Analysis
Supplementation adherence	Daily vitamin D_3 adherence will be <80% and loading dose vitamin D_3 adherence will be >95%	Self-report	Summary statistics of means and confidence interval.
		Count of pills	
Participant safety	Adverse events will be rare across all 4 treatment groups.	Adverse event	Summary statistics of proportions.
	Re-operations for a composite of fracture healing complications will follow the same 3 hypotheses as fracture healing.	Re-operations for a composite of fracture healing complications	Summary statistics of proportions.
	Levels of serum calcium will be similar across the 4 treatment groups. Levels of serum calcium will be within normal reference ranges.	Serum Calcium	Summary statistics of means and confidence interval.
	Levels of serum PTH will be similar across the 4 treatment groups. Levels of serum PTH will be within normal reference ranges.	Serum PTH	Summary statistics of means and confidence interval.
Protocol adherence	Protocol adherence will be acceptable.	Complete follow-up assessments including x-rays and bloodwork	Summary statistics of proportions.

Figure 1: Femur Fracture

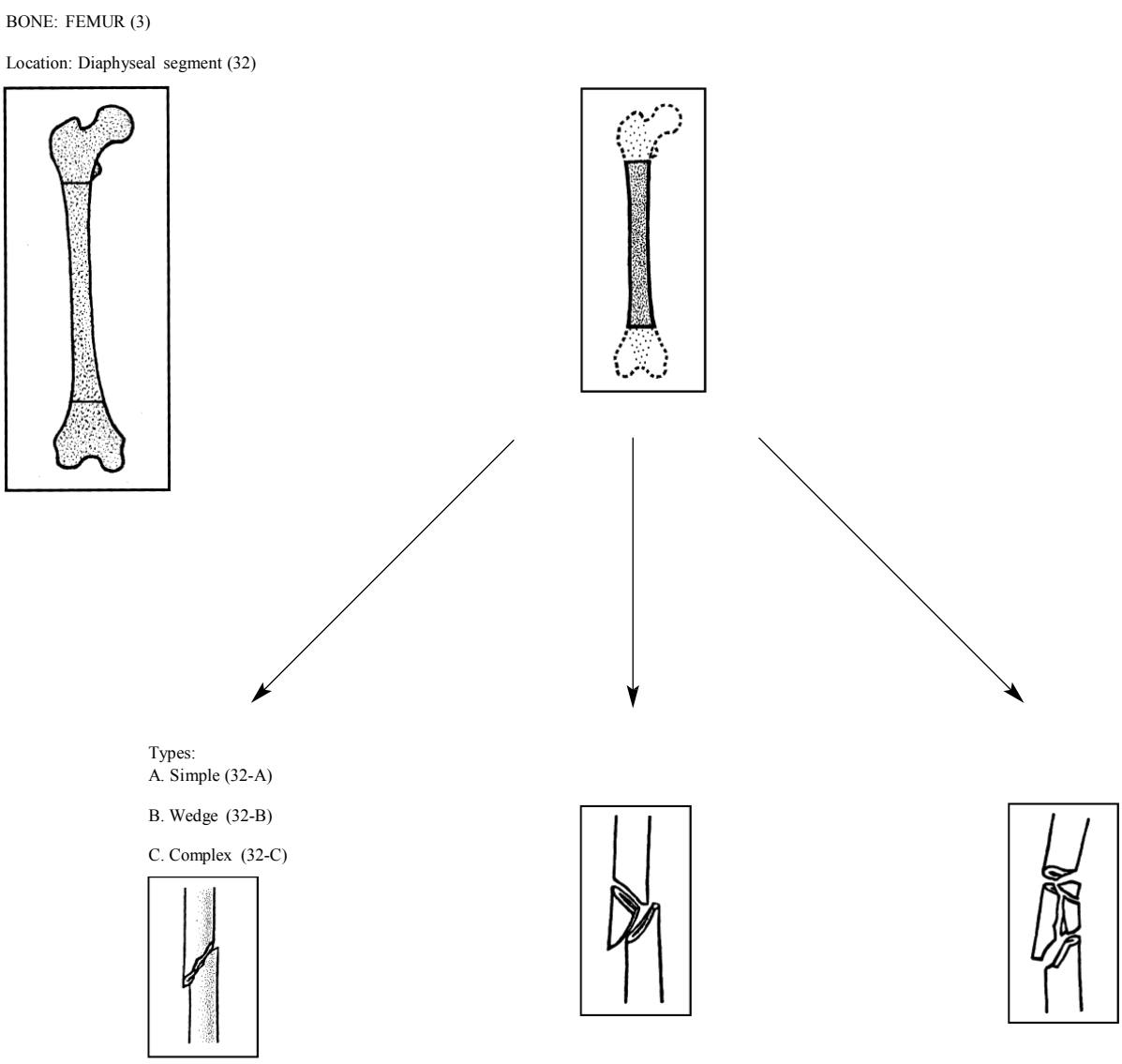

Figure 2: Tibia Fracture

BONE: TIBIA/FIBULA (4)

Location:
Diaphyseal segment (42)

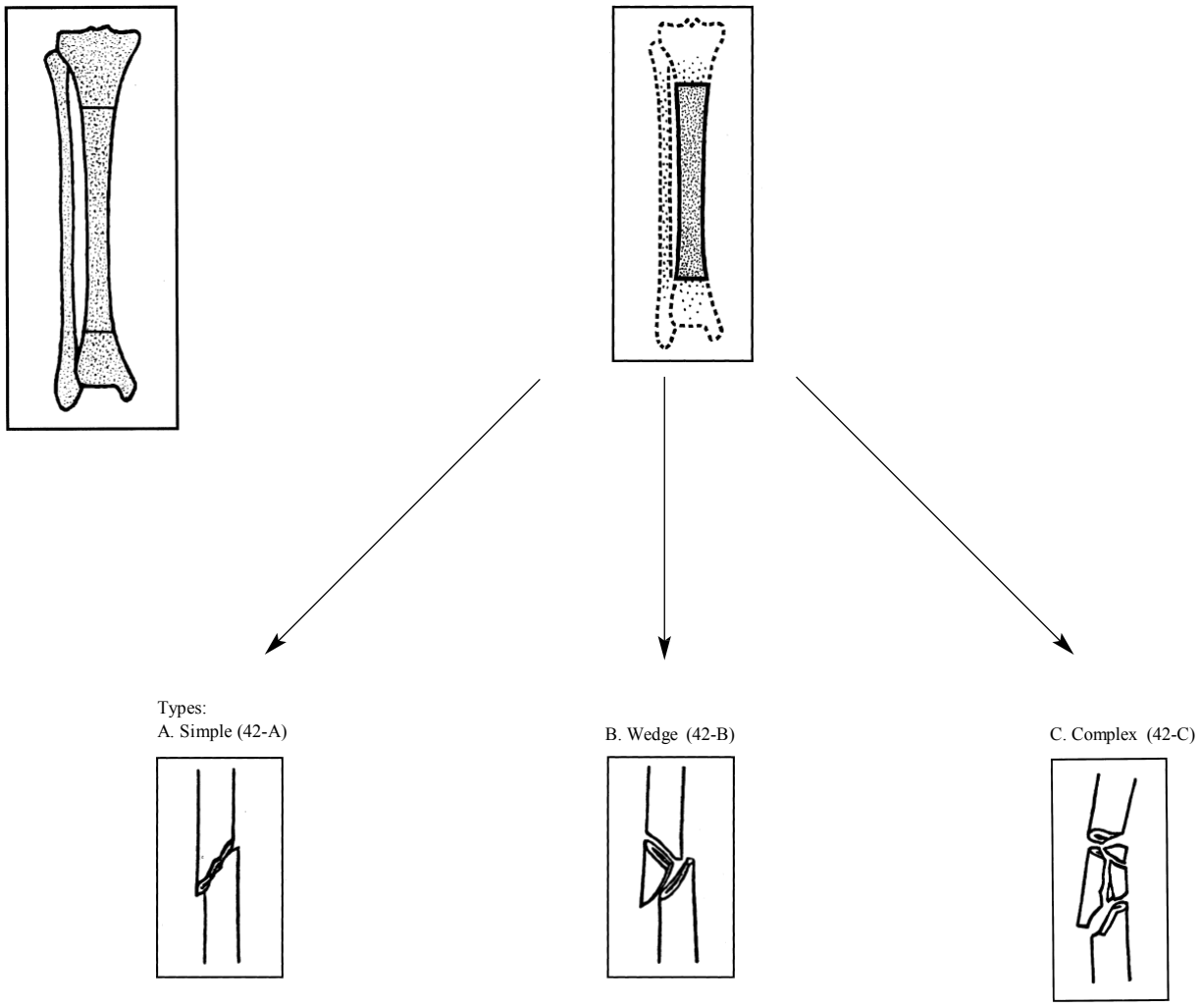

Figure 3: Unblinding of Personnel for Emergency Medical Management

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. The clinical research coordinator should contact the principal investigator (or designee) and provide details of the medical emergency as soon as possible after the event. The principal investigator (or designee) is responsible for reviewing and approving all requests for unblinding. At no time will the participant's health be compromised or medical treatment delayed.
3. Once approved, the clinical research coordinator (or designee) will contact the unblinded Project Manager and request the participant's treatment allocation. The unblinded Project Manager will provide the clinical research coordinator 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.
4. The unblinded personnel are not to unblind the principal investigator or any blinded members of the study team unless deemed necessary by the principal investigator.
5. Study personnel must keep all information related to the individual unblinding cases confidential.
6. All cases of unblinding must be documented, including: study ID, date of unblinding, parties unblinded, and reason for unblinding.

Figure 4: 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 3 people at different addresses with whom the participants does not live who are likely to be aware of the participant's whereabouts. The clinical 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 3 months to maintain contact and obtain information about any planned change in residence.

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