Bone Loading Exercises versus Risedronate on Bone Health in Postmenopausal Women

NINR Protocol Number: 378-14-FB

NINR Grant Number:

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NINR Program Official: Lynn Hardy

TABLE OF CONTENTS

{This table uses the Table of Contents function in Microsoft Word that will automatically update headings and page numbers used in the body of the report. To update the Table of Contents and all cross-references in the document, press CTRL-A to select the entire document, then press F9.}

LIST OF ABBREVIATIONS

AE	Adverse Events
BCS	Breast Cancer Survivor
BMD	Bone Mineral Density
BSI	Bone Strength Index
BW	Body Weight
Ca	Calcium
CaD	Calcium + Vitamin D
CITI	Collaborative Institutional Training Initiative
CCORDA	The College of Public Health and Center for Collaboration on Research Design and Analysis
CLIA	Clinical Laboratory Improvement Amendments
CON	College of Nursing
CRC	Clinical Research Center
CSA	Cross-Sectional Area
CU	Creighton University
D	Vitamin D
DSCM	Data and Safety Monitoring Committee
DXA	Dual Energy Absorptiometry
ELISA	Enzyme-Linked Immunosorbent Assay
ET	Exercise Trainer
FRAX	Fracture Risk Assessment
FSH	Follicle-Stimulating Hormone
FQHC	Federally Qualified Health Center
HSA	Hip Structural Analysis
IA	Iowa
M	Month
N	Number (typically refers to subjects)
NE	Nebraska
NIH	National Institute of Health
NINR	National Institute of Nursing Research
NOCCC	North Omaha Community Care Council
NOF	National Osteoporosis Foundation
NTx	N-terminal Telopeptide

ONJ	Osteonecrosis of the Jaw
ORC	Osteoporosis Research Center
PARQ	Physical Activity Readiness Questionnaire
PHC	People's Health Center
pQTC	Peripheral Quantitative Computed Tomography
PI	Principal Investigator
PTH	Parathyroid Hormone
QCT	Quantitative Computed Tomography
RA	Research Assistant
RCT	Randomized Controlled Trial
RedCAP	Research Electronic Data Capture
Reps	Repetitions
RET	Research Exercise Trainer
RM	Repetition Maximum
RM-ANOVA	Repeated Measures Analysis of Variance
RN	Research Nurse
ROM	Range of Motion
RPE	Rate of Perceived Exertion
RSF	Research Support Fund
SAHP	School of Allied Health Professionals
SOCCC	South Omaha Community Care Council
ST	Strength/Weight Training
Steps	Steps each leg
TNMC	The Nebraska Medical Center
TSH	Thyroid Stimulating Hormone
UL	Upper Limit
UNMC	University of Nebraska Medical Center
US	United States
VCF	Vertebral Compression Fracture
Y	YMCA

PROTOCOL SUMMARY

Title:	Bone Loading Exercises versus Risedronate on Bone Health in Postmenopausal Women
Study moniker:	Heartland Osteoporosis Prevention Study (HOPS)
Précis:	This stratified random study will compare changes in bone strength (bone structure, formation, and bone mineral density) at the hip and spine in women who take 12 months of either: 1) optimal calcium and vitamin D alone; 2) the bisphosphonate "risedronate" with calcium and vitamin D; or 3) a bone-loading exercise program with calcium and vitamin D.
Objectives:	Our long-term goal is to contribute development of clinical practice guidelines for the promotion of bone health in postmenopausal women with low bone mass, thus reducing the personal and societal burden of osteoporotic-related fractures.
	Specific Aims: Aim1: To compare Control, Risedronate, and Exercise group subjects on changes in bone structure at the tibia (bone strength index [BSI]: pQCT) and hip (femoral neck and shaft, intertrochanteric) (hip structural analysis: [HSA: DXA]) at baseline, 6, 12 months. Aim2. To compare Control, Risedronate, and Exercise group subjects on changes in BMD at the total hip, femoral neck, and spine (DXA) at baseline, 6, 12 months. Aim3: To compare Control, Risedronate, and Exercise group subjects on changes in bone formation and resorption at baseline, 6, 12 months. (formation: AlkphaseB, resorption: Serum NTx). Aim4: To explore relationships between adherence to exercise (%sessions attended) or adherence to risedronate (% pills taken) and changes in bone structure at the tibia (BSI) and hip (HSA).
Population:	A total of N = 246 subjects are needed to achieve the proposed objectives. The subjects will be randomized and evenly allocated across three groups. In order to account for a realistic amount of attrition (20%), **N = 309** participants will be recruited for this study so that at least N = 246 should be retained if 20% of participants do not complete the study. In order to enroll 309 participants who meet criteria for the study, we are expecting to screen 900 women for eligibility. All subjects must: a) be women who are in their first 5 years of menopause *(Menopause will be defined as either not having had a menstrual period in 12 months or having had both ovaries removed. In addition, FSH testing will be conducted on women who are unsure of their menopause status)*; b) weigh 300 pounds or less; c) not use medications or have diagnoses that

	would interact with the individual's ability to adhere or safely complete any of the study components; d) have a T score between 1 and -2.49 at the femoral neck, total hip, or L1-L4 spine skeletal sites as measured by Dual Energy Absorptiometry (DXA); f) be 19 years of age or older; and g) have their health care providers permission to enroll in the study.
Number of Sites:	Intervention implementation and data collection will take place at the following sites: • University of Nebraska Medical Center • The Nebraska Medical Center • Creighton University Medical Center, Osteoporosis Research Center • Omaha, Lincoln, and Council Bluffs-based YMCAs Additionally, we will be contacting large organizations in Omaha, such as Mutual of Omaha, as well as community centers, medical facilities, etc. to determine interest in advertising this research study at their facilities. Therefore, information for recruitment purposes will be available to potential subjects at entities which choose to advertise information about the Heartland Osteoporosis Research Study.
Description of Intervention:	This proposed study has a randomized 3-group (2 treatment groups & 1 control group), repeated measures experimental design. A computer generated code will be used to stratify subjects by exercise at baseline and then randomized to 3 groups (Control: n =103; Risedronate: n =103; Exercise: n =103) with assignments placed in sealed opaque envelopes for sequential use. All subjects will take dosages of calcium citrate supplements sufficient to ensure their total daily calcium (diet+supplements) is ~ 1200 mg daily and vitamin D^3 supplements with daily dose to ensure serum levels of vitamin D [25 (OH)D] are between 30 ng/mL and 80 ng/mL(optimal CaD). Subjects randomized to the Risedronate group will take optimal CaD daily and 150mg of oral risedronate once monthly for 12 months but will not participate in the exercise program. Subjects randomized to the Exercise group will take optimal CaD and also participate in 12 months of a bone-loading exercise program three times weekly at a local community-based YMCA (Y). To ensure the bone outcomes were not due to the CaD supplementation, a group taking only optimal CaD will serve as a control. While only women in the exercise group will participate in the structured bone-loading exercise program developed for this study, all women will be encouraged to participate in exercises and will be informed of the benefit of weight bearing and resistance exercises. The primary outcome will be bone structure at the tibia and hip and secondary outcomes are bone mineral density (BMD) and bone turnover. Repeated measures of primary and secondary outcome variables will be conducted at baseline, 6 and 12 months to better understand response to intervention components with a

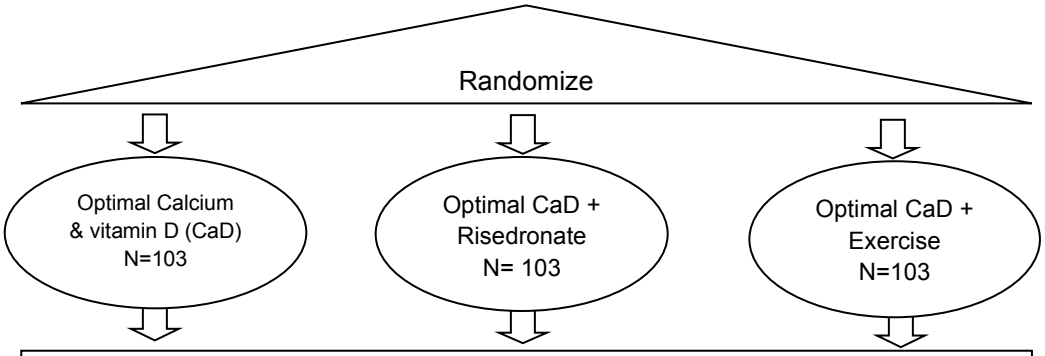
	maximum difference expected at 12 months. An exercise intervention lasting 12 months or 2 to 3 bone turnover (resorption / formation) cycles is necessary in order to measure the effects of training on bone outcomes.
Study Duration:	Time from subject enrollment to completion of analysis is 4 years and 6 months.
Subject Participation Duration:	Each subject will be asked to participate in the study for a total of 12 months.
Estimated Time to Complete Enrollment:	Study enrollment will begin in Year 1, month 6 and continue through Year 4, month 9.

SCHEMATIC OF STUDY DESIGN:

See *Protocol 1.Timeline for Data Collection*, for details regarding collection of specific measures

Prior to Enrollment

Prescreening: Prescreening form and PARQ
Screening:
Eligibility assessed by tests performed in the following order: 1) DXA; 2) laboratory analysis of CBC, serum vitamin D, calcium, creatinine, parathyroid hormone. Analysis of follicle stimulating hormone and/or thyroid stimulating hormone performed if necessary (See Section 7.1); 3) Fracture Risk Assessment; 4) Provider permission for participation



Baseline: Perform baseline assessments

3 months: Assessments of subject compliance and evaluation of supplement dose

6 months: Follow-up assessment of baseline outcome measures and safety

12 months: Post-Intervention assessments of outcome measures and safety

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2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Osteoporosis is a disease of fragile bones (decreased bone strength) and low bone mineral density (BMD). Approximately 18% of women with osteoporosis suffer a hip fracture and 22% die within a year of their fracture (1-3). Over 36 million post-menopausal American women have low bone mass (BMD T-scores -1 to -2.49) which increases their risk for osteoporosis (BMD T-scores -2.50 or lower) (2). Improving bone strength and preventing further loss in BMD is critical in post-menopausal women with low bone mass as it is difficult to build significant bone without the influence of estrogen (4). Preventative treatments are especially important during the first five years post-menopause because women lose 2% of their BMD per year during this time. Calcium (Ca), vitamin D (D) and exercise are recommended for prevention of osteoporosis (5) and bisphosphonates (BPs) are prescribed to improve BMD in women with diagnosed osteoporosis (6). BPs may also be prescribed for women with low bone mass who are not yet osteoporotic, but are more controversial in this population due to the potential for adverse effects with their long-term use (7,8). Also, the best predictor of fracture is bone strength, and strength is determined by bone structure as well as BMD. While BPs are effective in improving bone density, findings on the effectiveness of BPs in improving bone structure are inconsistent (9). A bone loading exercise program (high-impact weight bearing and resistance training) promotes bone strength by improving bone structure and by promoting bone formation at sites of mechanical stress as well as by preserving BMD. This randomized controlled trial (RCT) will compare changes after 12 months in bone structure, BMD, and bone turnover in post-menopausal women with low bone mass randomized to one control and 2 treatment groups (N =103 per group): 1) optimal calcium + vitamin D (optimal CaD) alone (Control); 2) BP plus optimal CaD (Risedronate); and 3) a bone loading exercise program plus optimal CaD (Exercise). Bone-loading exercise programs for post-menopausal women with low bone mass may more effectively improve bone structure than either BPs or optimal CaD alone (9). Prescribing exercise programs and delaying use of BPs may prevent adverse effects from long-term use of BPs, and provide the opportunity for later use of BPs when they may be critically needed (8,15). Results of this study could be used in developing a clinical management pathway for women with low bone mass at their peak period of bone loss that would involve lifestyle modifications such as exercises prior to medications such as BPs.

2.2 Rationale

Significance and Rationale for Sample Population. Osteoporosis and fractures result in significant morbidity and mortality in post-menopausal women with annual U.S. expenditures of approximately $19 billion (16-18). This problem will be even greater in the future, as the Surgeon General estimates the number of hip fractures in the United States could double or triple by the year 2040 (19). Our research aims to decrease the incidence of hip fractures by improving bone strength and preserving BMD in women with low bone mass (pre-osteoporotic) (20) during their first 5 years post menopause, a time of rapid and significant bone loss.

Comparing Effectiveness of Exercise with BPs on Bone Strength. Calcium and vitamin D, exercise, and BPs are all used to address bone health in post-menopausal women. There is strong evidence that adequate CaD through dietary intake and/or supplementation are necessary to maintain bone health (21-26). Although CaD are more effective than no treatment, it frequently is not enough to prevent

progression of bone loss or to prevent osteoporosis. BPs such as risedronate are the medications of choice for treatment of post-menopausal osteoporosis, and studies have reported that use of risedronate attenuates the bone loss associated with menopause in osteoporotic women (27). BPs improve BMD by inhibiting bone resorption. However, long-term use of BPs can result in a freezing of bone resorption and turnover with significant accumulation of micro- damage in bone (28). This micro-damage leads to increased risk of atypical hip and femur fractures (29-31). As a result, use of BPs in women with low bone mass is controversial, and providers are reluctant to prescribe BPs for greater than 5 years in women (32). Exercise programs combining resistance and high-impact weight bearing exercises can improve bone structure and increase bone formation at sites of mechanical stress (33) as well as maintain BMD. Participation in exercises improves the ratio of bone formation to resorption and improves bone structure by preserving trabecular and cortical structure, increasing thickness of cortical tissue, improving bone geometry and microarchitecture, and reorganizing bone collagen (34). Collagen reorganization during exercise maintains bone strength, even when BMD is decreased by as much as 10% (34). Participation in exercises is not associated with freezing of bone turnover, and furthermore, exercise is associated with many other positive effects for post-menopausal women including increased insulin sensitivity, improved functional ability and decreased risk of falls and depression (35). If an effective exercise program could substitute for, or delay the use of BPs in post-menopausal women with low bone mass, not only would bone health improve through the lifespan, but women would benefit from the many other positive effects of exercise.

Critical Need for Three Measures of Bone Strength. The gold standard for diagnosis of osteopenia and osteoporosis is BMD obtained from Dual Energy Absorptiometry (DXA) testing (36). However, the best predictor of fracture risk is bone strength. BMD is only one determinant of bone strength, and yet, most studies have relied on BMD as the sole measure for predicting fracture risk (37). Improved bone strength is a more realistic outcome for exercises than large increases in BMD (11). Greater increases in BMD have been reported with risedronate than with exercise in post-menopausal women. However, the magnitude of change in BMD may not equal the magnitude of change in fracture risk reduction. Marked reductions in fracture risk have been reported with small increases in BMD, likely because appropriate exercise training will improve bone strength as well as maintain BMD (38,39).
This study will include three measures of bone status because the strength of bone depends not only on the amount of bone present (BMD) but also on bone structure or geometry and on positive bone turnover rates (ratio of bone formation to resorption) (40,41). Bone structure refers to the cortical and trabecular network of bone that is vital for maintaining maximum bone strength (10,42). Compared to pre-menopausal women, both cortical thickness and trabecular bone volume in post-menopausal women are substantially reduced (43). In the proposed study, bone structure will be measured at the tibia and hip (femoral neck and shaft, trochanter). Bone strength index (BSI), will be measured at the 4%, and 66% tibial sites using peripheral quantitative computed tomography (pQCT). BSI is based upon the total bone area, tissue density, bone porosity, and distribution or shape (moment of inertia) at that bone site and has been found to be a strong predictor of the torsion and bending strength of bones (9). Bone structure at the hip will be measured using Hip Structural Analysis (HSA) software and DXA testing (10). HSA measures the distribution of bone mass at the hip. The specific data collected includes the cross-sectional area [CSA] occupied by bone mineral, an index of bone strength against compression; section modulus [Z, mm3], an index of bone strength against bending; and centroid [mm], the distance from the center of the mass to the periphery (10,44).

Bone turnover is the process of removing old bone (resorption by osteoclasts) and replacing it with new bone (formation by osteoblasts) (40,41). In this study, resorption will be measured by Serum NTx (nmol/BCE/L) and formation by AlkphaseB (U/C). One remodeling cycle of resorption and formation takes up to six months with maybe 5-15% of total bone mass replaced per year. Menopause results in a brief period (~5 years) of accelerated turnover with resorption far exceeding formation (45). Increased resorption will result in bone loss. With exercise, there is new bone formation in areas of mechanical strain resulting in bones with greater bending strength in those regions (46). While weakening mechanical properties of bone (such as decreased bending strength) are possible with long-term use of BPs (>5 years) (29-31,47), long-term participation in targeted exercise training continually improves mechanical properties of bone over time. This provides the rationale for the comprehensive examination of bone (bone structure, BMD, and bone turnover) proposed in the study.

This is one of few studies comparing the effectiveness of a bone-loading exercise program with BPs on bone strength. This is the first study to compare the efficacy of optimal CaD alone, or in combination with the BP, risedronate, or with combined resistance and weight-bearing exercises in improving bone structure and turnover and preserving BMD in women with low bone mass during the first 5 years post menopause. These comparisons are critical because they will determine whether standard practice should include a trial of lifestyle modification prior to BP prescriptions in this at risk population. Clinical management pathways for women who are at risk for other chronic illnesses such as hypertension or diabetes include trials of lifestyle modifications prior to prescriptions for medications. With the potential for adverse effects with long-term use of BPs and the potential bone strength benefits of exercise, studies should be conducted to determine if prescriptions for exercises are warranted prior to prescriptions for medications.

This study will use a comprehensive evaluation of bone strength, bone structure, BMD and bone turnover- in comparing the efficacy of optimal CaD alone, with BPs, or with exercises. We believe that the impact of exercises on bone health has been underestimated because researchers have placed too much emphasis on BMD (48).

This is the first study to optimize both calcium and vitamin D dosage. Our preliminary data and previous studies of others suggest that the efficacy of both BPs and exercises are improved with use of optimal CaD. Our results will provide more data on dosages of calcium required by post-menopausal women to supplement their dietary intakes, and dosages of vitamin D required for post-menopausal women to maintain serum levels at $\geq$30 ng/ml.

Our results will provide more information on adherence to exercise in post-menopausal women with low bone mass and on use of cognitive/behavioral strategies including education, goal-setting, reducing barriers, and graphic feedback to promote adherence to exercise.

This study was informed by findings on the efficacy of risedronate and resistance exercises in preserving BMD in post-menopausal women with low bone mass in our previous study, concerns about adverse effects with long-term use of BPs, the importance of other measures for bone health such as bone structure and turnover, studies reporting the high prevalence of vitamin D insufficiency in post-menopausal women, and new information on the importance of optimal dose of vitamin D.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

Risk of muscle soreness or injury with exercises.
There may be temporary muscle soreness for up to two days following the initiation of, or increase in resistance training or bone loading exercises. Sudden forceful movements (seldom associated with progressive and monitored exercise programs) are the most common cause of musculoskeletal injury associated with exercise. In the previous RO1 study, some exercise subjects (< 10%) did complain of temporary muscle soreness with initiation of exercises or increase in weights lifted. If subjects complained of discomfort beyond the expected muscle soreness, exercises were not performed until the discomfort resolved. When subjects resumed exercises, they began with adapted exercises and lighter weights after another session with the YMCA Exercise Trainer (YET). No serious adverse effects occurred in the 110 subjects participating in exercises in the previous R01.

Important precautions have been specified for this protocol to minimize and decrease the likelihood of any risk associated with the exercise program. Precautions include formulation of specific inclusion and exclusion criteria and monitoring of subjects for safe performance of exercises. In addition, the exercise program is initiated slowly and gradually, and the estimated 1 repetition maximum (1 RM) testing is not completed until week 2, providing the body time to acclimate to strength training before the max testing is performed. If subjects complain of discomfort or pain from the exercise program (more than the expected muscle soreness) the on-site YETs will seek consultation with the Research Exercise Trainer (RET) and Dr. Laura Bilek, Physical Therapist, and if necessary, refer subjects to their health care provider. The RET and Dr. Laura Bilek, PT, will make the decision to discontinue the exercise program after consulting with the health care provider and considering the desires of the subject. Generally, subjects will not discontinue exercises because of musculoskeletal problems, but this would be dependent on the nature and severity of the problem and the desires of the subject. If the musculoskeletal problem and/or persistent pain is/are not resolved, the subject may discontinue the exercise program. This subject will be considered off-protocol and will be asked to complete all tests and measurements as scheduled in alignment with intent-to-treat principles.

If the problem and/or pain is/are resolved, subjects will be encouraged to resume the exercises. Subjects who are resuming their exercise program may need to begin with lighter weights, will need a consultation with the RET, and may require another supervised session with the RET and/or Dr. Bilek.

Risk of cardiovascular events with exercises.
There is a small risk of a cardiovascular event with exercise in persons with preexisting cardiovascular disease. The incidence of death during vigorous exercise in healthy adults is 1/15,000 to 18,000 per year. Exercise training is performed at a moderate intensity which has a much lower risk of cardiac events than vigorous exercise.

The following precautions have been specified to reduce the infrequent risk of cardiovascular events with exercises:

- Subjects will be assessed for cardiac risk with the Physical Activity Readiness Questionnaire (PAR-Q) prior to study enrollment and those with high risk will be excluded from the study.
- Approval from the health care provider is required prior to study enrollment
- Study personnel (Research Project Coordinators (RPCs) or RET) will obtain blood pressures on all subjects at baseline, 6, and 12 months and will consult with the subjects provider for those with blood pressure greater than 140/90
- RETs and on-site YETs will be CPR certified
- All YMCAs are equipped with cardiac defibrillators

No cardiovascular events occurred with women participating in exercises in the previous R01, and age range for subjects was 35 years to 75 years.

Risk of fractures with exercises.

Although the risk is much less than for patients with osteoporosis, patients with low bone mass are at increased risk of fracture, most notably, vertebral compression fracture (VCF). Movements most likely to precipitate a VCF are combined spinal flexion and rotation with load. So picking up a heavy object with one hand would be especially problematic. To minimize risk, we will:

- minimize use of free weights and the need to lift heavy objects from the floor
- use strength training machines that assist in stabilizing the body during the lifting motions
- provide education on correct, upright posture during performance of all exercise to avoid loaded spinal flexion

Risk of calcium supplementation.

The Tolerable Upper Limit (UL) (highest level of daily intake of calcium from food, water and supplements that is likely to not pose any risks of adverse health effects for almost all of the general population) is currently established as greater than 2,500 mg per day. Risks of intake above the UL include hypercalcemia, impaired kidney function and decreased absorption of other minerals (iron, zinc, magnesium and phosphorus). Dietary intake of calcium will be monitored at baseline with the National Osteoporosis Foundation (NOF) Calcium Intake Estimate tool, and supplements will be prescribed to ensure subjects obtain approximately 1200 mg of total calcium (diet and supplements) daily which is well below the UL. In addition, serum calcium levels will be drawn at baseline. Kidney stones have occurred with high intakes of calcium, therefore, a daily fluid intake of at least 2,000 ccs will be encouraged. Participant will be counseled verbally and in writing not to take additional supplements of calcium beyond the study protocol to keep their intake below the UL.

Risk of Vitamin D supplementation.

Excessive amounts of vitamin D (D) can result in hypercalcemia. The current Recommended Daily Amount of D is 400-800 IU/day (or 2,800 to 5,600 per week), but studies have reported that D supplements of 4,000 IU per day are safe. In addition, subjects will be monitored for signs of D toxicity, i.e. hypercalcemia (nausea, vomiting, poor appetite, constipation, weakness and weight loss) at RPC visits throughout the study. At baseline, subjects will be prescribed optimal doses of D based on the

following protocol: Subjects who have serum D levels at 30 ng/ml or greater will be prescribed 1,000 IU daily; subjects with levels of 20-29 ng/ml will be prescribed 2,000 IU daily; and subjects with levels of 10-19 ng/ml will be prescribed 3,000 IU daily. Subjects receiving 3,000 IU daily will have their serum levels rechecked at 3 months. Subjects will serum D level ≥ 60 ng/ml at screening will have levels rechecked at 3 months, as well as calcium and albumin (calcium adjusted for albumin). All other subjects will have follow-up serum levels at 6 months.
Participants will be counseled verbally and in writing not to take additional supplements of D beyond the study protocol to keep their intake below the UL. Subjects with a serum 25(OH) D level at baseline < 10 ng/ml will be excluded from the study and can reapply when their serum levels are within normal limits. Participants with serum vitamin D greater than 60ng/ml at the time of screening will have serum levels rechecked at 3 months as well as analysis of serum calcium adjusted for albumin. If substantive problems occur related to administration of calcium or D or if serum levels of D elevate beyond acceptable levels, subjects will be asked to discontinue the supplements and will be referred to their health care provider for recommendation.

Risk of risedronate.

Reported adverse effects of BPs, including risedronate, are rare, but do include local damage to the mucous membrane, gastrointestinal bleeding, abdominal pain, perforating ulcers, vomiting, esophagitis, esophageal cancer, renal impairment at certain doses, severe bone, muscle, and joint pain, and atrial fibrillation (62). One serious adverse effect that was first reported with use of the BP zoledronic acid in high doses in cancer patients is osteonecrosis of the jaw (ONJ) (63).While short-term use of BPs is relatively safe for most women, the safety of long-term use of BPs (greater than five years) is unclear (64). The FDA recommends that providers be aware of a possible risk of atypical hip fractures in patients taking BPs long-term.

To minimize adverse effects of risedronate, subjects will be instructed in the correct method for ingestion of the medication (upon arising in the morning with an 8 ounce glass of water or 2 hours after the last meal of the day, and subjects are to remain upright and have no oral intake except water for at least 30 minutes after taking risedronate). Serious side effects (recurring abdominal pain, gastritis, dysphagia or bone, joint, and muscle pain), will result in discontinuation of the drug. Subjects will be instructed to contact study personnel in the event of discomfort when taking this medication. RPC will confirm that the subject is taking medication as directed, and will ask Nancy Waltman PhD, APRN-NP or Jon Beck, Pharm.D to contact the participant if necessary. If the discomfort cannot be easily resolved, the subject will be referred to their health care provider for a decision on continuation of BPs.

Risk of increased bone loss.
Another concern is that postmenopausal women with low bone mass may experience more bone loss during the study and be at even greater risk for fractures (especially subjects in the control group). During the proposed study, DXA testing will be obtained at baseline 6, and 12 months, and all DXA results will be sent to the subjects' health care provider. If the subject has completed 6 months of the study and her BMD at the hip or spine has decreased to a T-score of -2.5 or below, the health care provider may decide to prescribe treatment with medications such as bisphosphonates. Subjects in the control or exercise groups who begin taking bisphosphonates during this study will be considered off-protocol but will be asked to continue to participate in all testing for the study as scheduled.

PQCT and DXA testing.
There is some radiation exposure with quantitative computed Tomography (QCT) testing, especially with axial QCT exams. Radiation doses received during a peripheral QCT (pQCT) exam (2.46 uSV) are much less than radiation dosages from axial QCT exams (30 60 uSV) or from radiation obtained annually from background radiation (2500 uSV). Risks associated with DXA bone density testing are minimal. DXAs are safe, non-invasive and painless. Subjects will have a DXA of the whole body at baseline, during which the subject is exposed to 20uSV, or a similar amount you would receive during a 2 hour airplane flight. Subjects will have a DXA of the hip and spine at 6 and 12 months, during which the subject is exposed to 4.8uSV at each scan, or approximately 10% of the radiation required in a mammogram.

Risks associated with obtaining blood and serum specimens.
Risks from drawing blood are minimal with the most common being bruising or hematoma formation at the venous access site. This is minimized by proper technique and by the application of pressure at the site. A rare complication of obtaining serum specimens is infection at the venous access site. This is minimized with the use of sterile gloves, sterile needles, and antibacterial cleansing of the skin prior to the venipuncture. All venipuncture will be performed by experienced research nurses at the UNMC Clinical Research Center or trained study personnel to maintain quality, minimize variation in procedure and risk of infection.

Risk of psychological discomfort.
Risks associated with completing the questionnaires and journal include the potential for mild psychological stress related to questions on the forms. Subjects will be informed that they can refuse to answer any question that may be upsetting to them.

Risk of loss of confidentiality.
While not always possible, all measures will be taken to protect the subject's identifiable and protected health information and research data.

2.3.2 Potential Benefits

Subjects may receive no benefits from participation in the study. No benefit is guaranteed. However, subjects with low bone mass who are at high risk of developing osteoporosis and osteoporotic fractures may improve bone structure and turnover and preserve BMD with optimal CaD alone, risedronate, or bone loading exercises. Subjects may benefit from receiving information on low bone mass and on effective interventions for improving bone health and prevention of osteoporosis

3 OBJECTIVES

3.1 Study Objectives

Our **long-term goal** is to contribute to the development of clinical practice guidelines for the promotion of bone health in postmenopausal women with low bone mass. Our **central hypothesis** is that improvements in bone health will be greater in subjects randomized to the Exercise group compared to subjects in either the Control or Risedronate groups.

Aim1: To compare Control, Risedronate, and Exercise group subjects on changes in bone structure at the tibia (bone strength index [BSI]: pQCT) and hip (femoral neck and shaft, intertrochanteric) (hipstructural analysis: [HSA: DXA]) at baseline, 6, 12 months.
H1a: At 12 months, there will be significantly greater improvements in bone strength index (BSI) at the 4% tibial site in Exercise subjects compared to subjects in either Risedronate or Control groups
H1b: At 12 months, there will be significantly greater improvements in bone mass distribution (HSA; centroid, mm) at the femoral neck in Exercise subjects compared to subjects in either Risedronate or Control groups

Aim2. To compare Control, Risedronate, and Exercise group subjects on changes in BMD at the total hip, femoral neck, and spine (DXA) at baseline, 6, and 12 months.
H2a: At 12 months, there will be significantly greater improvements in BMD at the total hip, femoral neck, and spine in Exercise and Risedronate subjects compared to subjects in the Control group
H2b: At least 80% of subjects in both the Exercise and Risedronate groups will have preserved BMD at the total hip, femoral neck, and spine.

Aim3: To compare Control, Risedronate, and Exercise group subjects on changes in bone formation and resorption at baseline, 6, 12 months. (formation: AlkphaseB, resorption: Serum NTx).
H3a: At 12 months there will be significantly greater decreases in serum markers of bone resorption (Serum NTx) in subjects in the Exercise and Risedronate groups compared to subjects in the Control group
H3b: At 12 months, mean Serum NTx levels for subjects in both Exercise and Risedronate groups will have decreased to levels considered at low risk for fracture (< 12.6 nmol BCE/L)
H3c: At 12 months, there will be significantly greater improvements in serum markers of bone formation (Alkphase B) in Exercise subjects compared to subjects in either Control or Risedronate group subjects

Aim4: To explore relationships between adherence to exercise (%sessions attended) or adherence to risedronate (% pills taken) and changes in bone structure at the tibia (BSI) and hip (HSA).

3.2 Study Outcome Measures

3.2.1 Primary

Bone structure will serve as the primary outcome for this study and will be measured using peripheral quantitative computed tomography (pQCT) and Hip Structural Analysis (HSA) at baseline, 6 and 12M. PQCT will measure bone strength index (BSI) at the 4% and 66% tibial sites. BSI is based upon the total bone area, tissue density, bone porosity, and distribution or shape (moment of inertia) at that bone site and has been found to be a strong predictor of the torsion and bending strength of bones.(9) Bone structure at the hip will be measured using HSA software and DXA testing.(10) HSA specifically measures the distribution of bone mass at the hip. The data collected includes the cross-sectional area (CSA) occupied by bone mineral, an index of bone strength against compression; section modulus (Z, mm_3), an index of bone strength against bending; and centroid (mm), the distance from the center of the mass to the periphery.(10, 45)

3.2.2 Secondary

Bone turnover and BMD will serve as secondary outcomes and will be measured at baseline 6 and 12M. Bone turnover will be measured by Serum NTx (nM BCE) and AlkphaseB (ng/ml). BMD will be measured using DXA.

4 STUDY DESIGN

This study has a stratified, randomized 3-group (2 treatment groups & 1 control group), repeated measures experimental design. A computer generated code will be used for randomization to 3 groups (Control: n =103; Risedronate: n =103; Exercise: n =103) with assignments placed in sealed opaque envelopes for sequential use. All subjects will take dosages of calcium citrate supplements sufficient to ensure their total daily calcium (diet+supplements) is ~ 1200 mg daily and vitamin D^3 supplements with daily dose to ensure serum levels of vitamin D [25 (OH)D] are between 30 ng/mL and 80 ng/mL(optimal CaD). Subjects randomized to the Risedronate group will take optimal CaD daily and 150mg of oral risedronate once monthly for 12 months but will not participate in the exercise program. Subjects randomized to the Exercise group will take optimal CaD and also participate in 12 months of a bone-loading exercise program three times weekly at a local community-based Y. To ensure the bone outcomes were not due to the CaD supplementation, a group taking only optimal CaD will serve as a control. We believe it would be unethical for women at risk for further bone loss to have restrictions in physical activity for 12 months. Thus, while only women in the exercise group will participate in the structured bone-loading exercise program developed for this study, all women will be encouraged to participate in exercises and will be informed of the benefit of weight bearing and resistance exercises. **The primary outcome will be bone structure at the tibia and hip and secondary outcomes are BMD and bone turnover**. Repeated measures of primary and secondary outcome variables will be conducted at baseline, 6 and 12 months to better understand response to intervention components with a maximum difference expected at 12 months. An exercise intervention lasting 12 months or 2 to 3 bone turnover (resorption / formation) cycles is necessary in order to measure the effects of training on bone outcome

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 Subject Inclusion Criteria

All subjects must: a) be women who are in their first 6 years of menopause *(Menopause will be defined as either not having had a menstrual period in 12 months or having had both ovaries removed. In addition, FSH testing will be conducted on potential participants who are unsure of their menopause status)*; b) have a T score between 1 and -2.49 at the femoral neck, total hip, or L1-L4 spine skeletal sites as measured by DXA; c) be 19 years of age or older; and d) have their health care providers permission to enroll in the study.

5.2 Subject Exclusion Criteria

Subjects will be excluded if they: a) have a 10 yr probability of hip fracture > 3% or major fracture >20% based on results of the FRAX tool; b) are currently taking or have taken bisphosphonates within the past 6 months, estrogen replacement therapy, drugs affecting bone such as tamoxifen or aromatase inhibitors; c) weigh $\geq$300 lbs; d) serum 25(OH)D < 10 ng/ml e) have Pagets disease, heart disease, uncontrolled hypertension, renal disease, chronic fatigue syndrome, herniated disc, severe peripheral neuropathy, severe osteoarthritis, severe acid reflux or other concomitant conditions that prohibit participation in exercises, risedronate therapy, or use of CaD supplements; or f) have a T score below -2.49 at the femoral neck, total hip, or L1-L4 spine skeletal sites as measured by DXA

In the event of abnormal lab values at screening, personnel will consult Dr. Lynn Mack on appropriateness and safety of participation in the main study.

Strategies for Recruitment and Retention

Recruitment fliers and other print materials (see relevant attached documents) will be placed in physician and/or practitioner offices and community centers, and the principal investigators, RPCs (research project coordinator), RET (Research Exercise Trainer), RA (research assistant), and minority recruiter will solicit subjects during group presentations. In addition, subjects will be recruited through newspaper, radio ads, billboards, on-campus "electronic boards", via the Creighton University ORC's mailing list (women who have indicated interest in participating in future research), website and Facebook page. The website and Facebook page will be developed upon initiation of the project. In addition, we will utilize products such as pens, t-shirts, tote bags, etc. for advertising. No information will be distributed for viewing by potential subjects without prior IRB approval. Potential subjects will be provided a phone number or email to notify RPCs of their interest in the study. They will be interviewed by telephone by study personnel. They will be screened for eligibility and provided more information about the screening and main studies. Participants can also be screened for eligibility electronically by accessing the study website. If they meet the criteria for the study a screening study consent form/main study consent form, an informational handout regarding the research study (see One Page Study Summary form), a copy of "What do I need to know before being in a research study", and "The rights of research subjects" will be sent to these potential subjects. After 1-2 weeks, the RPCs or one of the principal investigators will meet with the subject at a face-to-face visit, follow the procedure for informed consent, and the potential subject will then be asked to sign a screening consent form for lab and diagnostic testing. Subjects will not be allowed to sign the screening consent form unless it is determined they are aware of the basic requirements of the main study.

5.3 Treatment Assignment Procedures

A computer generated code will be used for randomization to 3 groups (Control:n =103; Risedronate: n =103; Exercise: n =103) with assignments placed in sealed opaque envelopes for sequential use.

5.4 Subject Withdrawal

5.4.1 Reasons for Withdrawal

Subjects are free to withdraw from participation in the study at any time upon request.

An investigator may terminate a study subject's participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject.
- Laboratory values change to where medication is now needed and subject no longer qualifies for the group they were randomly assigned to
- Musculoskeletal problems and/or pain occur and it is no longer safe for subject to continue with exercise protocol

5.4.2 Handling of Subject Withdrawals or Subject Discontinuation of Study Intervention

If taken off protocol for whatever reason, we will still ask subjects to complete all tests and measurements as scheduled in alignment with intent-to-treat principles. There will be no extra attempt made to replace the subject as attrition is accounted for in the total number recruited and consented.

5.5 Premature Termination or Suspension of Study

This study may be suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the principal investigator will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination include, but are not limited to:

- Less than 50 subjects are accrued for each group within the 42 month recruiting period.
- >10% of the subjects develop serious adverse events related to optimal CaD, risedronate, ore exercises.
- 50% attrition of subjects in either group occurs including BMD T-scores falling below -2.5.

6 STUDY INTERVENTION

6.1 Intervention(s) Description

All subjects will take dosages of calcium citrate supplements sufficient to ensure their total daily calcium (diet + supplements) is ~1200 mg daily and will take vitamin D_3 supplements with daily dose dependent on their serum levels of vitamin D (25 [OH]D) (optimal CaD). Subjects randomized to the Risedronate group will take optimal CaD daily and 150 mg of oral risedronate once every 4 weeks for 12 months but will not participate in the exercise program. Subjects randomized to the Exercise group will take optimal CaD and also participate in 12 months of a bone-loading exercise program three times weekly at a local community-based Y. To ensure the bone outcomes were not due to the CaD supplementation, a group taking only optimal CaD will serve as a control. The primary outcome will be bone structure at the tibia and hip and secondary outcomes are BMD and bone turnover. Assessors of these variables will be blinded to subject group. Repeated measures of primary and secondary outcome variables will be conducted at baseline, 6 and 12 months to better understand response to intervention components with a maximum difference expected at 12 months.

6.2 Administration of Intervention

Optimal CaD

All subjects will take calcium citrate supplements daily to ensure total intake (dietary and supplement) is ~1200 mg. For optimal bone health, serum vitamin D levels are equal to or > 30 ng/ml. In the proposed study, all subjects will be prescribed optimal doses of vitamin D based on their serum 25(OH) D levels with a goal of reaching optimal serum levels of 30 ng/ml. To determine the optimal dose of D, serum 25 (OH)D measures will be obtained for all subjects at baseline. Subjects who have serum D levels at 30 ng/ml or greater will be prescribed 1,000 IU daily; subjects with levels of 20-29 ng/ml will be prescribed 2,000 IU daily; and subjects with levels of 10-19 ng/ml will be prescribed 3,000 IU daily. Subjects receiving 3,000 IU daily will have their serum levels rechecked at 3 months. Participants with serum vitamin D greater than 60ng/ml at the time of screening will have serum levels rechecked at 3 months as well as analysis of serum calcium adjusted for albumin. All other subjects will have follow-up serum levels at 6 months. Time periods for assessing serum D were chosen because studies have reported that with daily dosing of D, it may take three months for plateau serum levels to be reached. The serum D criteria pertain to all 3 treatment groups. Patients with serum levels < 10 ng/ml have severe D deficiency, will be excluded from the study, and referred to their health care provider for management.

See *Protocol 2. CaD Delivery_RPC Responsibilities*

Risedronate

Risedronate is a pyridinyl bisphosphonate with potent anti-resorptive activity which is approved at various dosages for the prevention and treatment of post-menopausal osteoporosis. Risedronate subjects will take 150 mg of oral risedronate monthly plus optimal CaD. Study personnel will contact subjects monthly to remind them to take their risedronate tablet. The National Osteoporosis Foundation (NOF) recommends that BPs be prescribed for all patients with vertebral or hip fractures, femoral neck

or spine T-scores of <-2.5 (dx of osteoporosis), and a 10-year high risk probability of fracture based on results of the Fracture Risk Assessment (FRAX) tool). The FDA recommends that providers be aware of a possible risk of atypical hip fractures in patients taking BPs long-term. Discontinuation of BPs after five years of treatment is becoming a common practice, particularly for patients at low risk of fracture.

See *Protocol 3. Risedronate Delivery_RPC Responsibilities*

Medication Calendar Cards

CaD tablets will be supplied in Medication Calendar cards and dispensed by The Nebraska Medical Center (TNMC) outpatient pharmacy to study personnel. Calendar cards will be stored in Dr. Bilek's lab, in a locked cabinet and distributed to subjects at 3-month intervals. Medication Calendar cards, each containing a four-week supply of Ca and a second card containing D, will be distributed via mail or in person. Subjects in the risedronate group will receive additional cards containing risedronate. The medication risedronate requires a prescription. Prescriptions for risedronate will be written by Lynn Mack, MD (who serves as supervising physician on the study), dispensed to study personnel by TNMC outpatient pharmacy, and mailed to subjects or delivered in person. Tablets will be secured in individual bubbles on the cards. Subjects will be instructed to take their risedronate tablet at a minimum of seven days prior to the next scheduled dose (see *Form 1. Calendar Card Instructions*). All cards will be collected by study personnel or returned by postage paid mail after each 4-week period. In circumstances which a participant does not wish to take study supplements, and would like to continue taking their own, personnel will monitor their adherence to taking optimal levels of calcium and vitamin D through taking their own vitamins and/or supplements (see *Form 2. Blank Calendar*).

Bone-Loading Exercise Program In the proposed study, exercise participants will receive CaD per protocol as described for the Risedronate and Control participants. In addition, exercise participants will participate in an exercise intervention consisting of 1) high impact weight bearing exercise such as jogging and 2) resistance exercises three times weekly for 12 months at a community-based YMCA (Y) (There are 8 Y's based in Omaha, NE, 3 in Lincoln, NE, and 1 in Council Bluffs, IA). Each session will include warm up and cool down exercises consisting of 5 minutes of slow walking.

Resistance Exercise (see *Form 3. HOPS Exercise Booklet_Revised* for details)

1) Upper Extremity Exercises - Push Exercises (2 sets each): horizontal press, overhead press.
2) Upper Extremity Exercises - Pull Exercises (2 sets each): latissimus pull, sitting row.
3) Lower Extremity Exercises: (2 sets each)
Group A (first six months): leg press, knee curl, and *side lunge
Group B (second six months): leg press, knee curl, and *forward lunge
4) Core Exercises: (2 sets each)
Group A (first six months): *pelvic tilt, *side bridge,*superman
Group B (second six months): *supine bridge, *side bridge, *pelvic tilt
(*indicates exercises using body weight for resistance.)

Exercises should be completed as follows (see *Form 3. HOPS Exercise Booklet_Revised)*: Participants will alternate between colored exercises, i.e. Red is Upper Body, Blue is Lower Body, and Green is Core to allow the participant an effective use of time and also meet the required 2 minute rest before performing the same exercise again. One day of recovery is required between exercise sessions. There is no set order that the exercises need to be completed in, as long as they are all completed and with 2 minutes of rest between the same exercises (see *Protocol 4. First Exercise Session Explanation and Documentation*)

Initial resistance during week 1 will be based upon % of body weight values for each machine weight exercise (*Form 4. Starting Load Values Based Upon Body Weight*) along with participant feedback using the Borg rate of perceived exertion (RPE) scale (see *Form 5. Borg RPE scale*). For body weight exercises, the participant will start out with the basic exercises options where offered. This acclimation of the machine weight exercises will prepare the participant for the estimated 1 RM testing that will occur during week 2. Week 2 will be used to determine loads for weight machines. Strength will be assessed by determining the maximum load that can be lifted for 9 or less repetitions with good form *(Protocol 5. Estimating 1RM)*. Progression will be prescribed based on the participant's estimated 1 RM value and the YET HOPS excel spreadsheet or progression tables (*Protocol 6. YET HOPS Exercise Schedule* or *Protocol 7. Progression and Increase Parameters for Exercise*). Reassessment of 1 RM will occur at 6 months. The purpose of 1 RM reassessment is to validate that the intervention is resulting in physiologic change and to evaluate if the workload is at a therapeutic potential (goal: workload ≥ 70%of 1RM). Participants will be encouraged to increase workload to ≥ 70% of 1 RM with a goal of reaching a resistance which results in volitional fatigue at 8-12 reps. Volitional fatigue is defined as the point at which the load cannot be lifted correctly with any additional repetitions. For those exercises using body weight for resistance, load will be added using a weighted vest, an advanced movement, or increased hold time. Both resistance and repetitions will be increased over time to participant tolerance.

Table 2. Resistance Training with Weight Machines: Exercise Progression

Week/Month	Resistance	Repetitions	Sets
Week 1	Self-selected	Progress to 15 reps	1
Week 2	40% 1 RM or self-selected from week 1 (whatever is greater)	Progress to 15 reps	2
Weeks 3-6	Increase 5-10% 1 RM/week	10–15 reps Increase load when reps=15	2
	Goal: 70% of 1 RM during Week 6-minimum therapeutic threshold for increasing BMD		
Week 7 - 12	Increase ~ 2-5%/week until volitional fatigue at 8–12 reps	Volitional fatigue at 8–12 reps	2
	Increase load when reps > 12 on 2 consecutive sessions Goal: Maintain resistance between 70–85% 1 RM		
6 & 12 months	Complete 1 RM testing Confirm load >70% 1 RM Increase if needed	Volitional fatigue at 8–12 reps	2

Table 3. Body Weight Resistance Training: Exercise Progression

Week/Month	Resistance*	Sets	Reps*
Weeks 1-2	0% BW	1	5-12
Weeks 3-4	0% BW	2	8-12
Month 2	1-2% BW	2	8-12
Month 3	2-5% BW	2	8-12
Month 4-12	5-10% BW	2	8-12
Increase load (% BW) when reps >12 on 2 consecutive sessions			

*BW=Body Weight; Reps=Repetitions

Impact Exercise-Jogging.

In addition to resistance exercise, the exercise intervention will include high impact, weight bearing exercises with high ground reaction forces to promote bone remodeling. Participants will walk around a track, or any other open space, interspersed with short periods of jogging. After walking for 20-30 seconds, participants will jog the prescribed number of steps and then return to walking. To avoid working at a vigorous intensity, participants will continue walking until they reach an RPE at or below 11 on the Borg RPE scale provided. (see *Protocol 8. Impact Jogging*)

Table 4. Impact Jogging Progression

Week/Month	Resistance*	Sets	Steps*
Weeks 1-2	0% BW	3-5	4-6
Weeks 3-4	0% BW	5-10	6
Month 2	0% BW	7-10	6-10
Month 3	1-3% BW	10	6-10
Month 4-5	3-5% BW	10	6-10
Month 6-8	5-7% BW	10	6-10
Month 9-12	7-10% BW	10	6-10

*BW=Body Weight; Steps=Steps Each Leg

To promote optimal performance, participants will be provided the *Form 3. HOPS Exercise Booklet_Revised* and *Form 8. Exercise Log_Revised*. The booklet will include detailed written and visual supportive instructions for each exercise including specific prescribed exercise session parameters to guide the participants. The exercise log applies corresponding colors to associate exercises with those in the booklet. The exercise log will also be a tool used to detail the prescribed resistance, repetitions, sets, and steps to assure the participant is meeting the goals set forth for them by the study.

To promote optimal adherence and therapeutic potential of workload, a graphic feedback sheet will be provided to the participant (see *Protocol 9. Graphic Feedback*). The graphic feedback sheet will display graphs of the individual's prior performance relative to study goals in order to improve adherence. For statistical analysis, adherence will be defined as the % training sessions attended; this will be calculated using the participant logs, which will be validated by Y electronic entrance documentation.

Exercise participants can perform exercises at the Ys at any time during operating hours regardless of whether one of the study's on-site YET coordinators are present (*Protocol 10. Exercise Trainer Oversight Schedule_Revised*). Even when YET coordinators are not present, other exercise specialists at the Y will always be present to answer general exercise questions or assist if problems arise with the exercise equipment.

All exercises will be performed at a Y under the direction of Y exercise trainers (YETs) (see *Form 10. YMCA Contact Sheet for Participants_Version 3*, *Form 11. Availability of YETs*). On-site YETs will communicate with each exercise participant every two weeks during the 12-month study, completing the *Form 12. YET Documentation Form* at each time of contact (see *Protocol 11.Storing Exercise Docs at YMCAs)*. Communication between the RET and YET will be ongoing and will occur at specific, along with intermittent, times during the study. The RET and YET's will also collectively use strategies regarding participant adherence to the exercise program (see *Protocol 12.Addressing Missing Exercise Session, Adherence*, *Protocol 13. Addressing Continued Exercise Non-Compliance*, *Protocol 14. Exercise Group_Addressing Withdrawn or Off-Protocol Participants*, *Protocol 15. Exercise Group_Addressing Problems on YET Doc Form*, *Protocol 16. Using Barrier Intervention Strategies*).
During the 12-month study, the RET will visit on-site YET coordinators every two months and will monitor their performance. Coupled with orienting all Y staff members and providing additional in-

depth training and supervision for on-site YET coordinators, the RET will be responsible for conducting the initial exercise participants training sessions during their first Y visit, performing the estimated 1RM testing, and helping maintain fidelity of the exercise intervention (see *Protocol 10. Exercise Trainer Oversight Schedule_Revised*
Protocol 11.Storing Exercise Docs at YMCAs
Protocol 12.Addressing Missing Exercise Session, Adherence
Protocol 13. Addressing Continued Exercise Non-Compliance
*Protocol 14. Exercise Group_*Addressing *Withdrawn or Off-Protocol Participants*
Protocol 15. Exercise Group_Addressing Problems on YET Doc Form
Protocol 16. Using Barrier Intervention Strategies
Protocol 17. RET Protocol for YMCA Exercise Sessions by Visit
Protocol 18. Scheduling YET Visits
Protocol 19. Storing Scanned-In Exercise Documents

6.3 Intervention Fidelity and Assessment of Compliance

Low adherence rates to exercises, risedronate, and CaD would impact fidelity of intervention components and limit generalizability of study results.

According to Bandura, adherence is related to "task and barrier self-efficacy". Task self-efficacy is subject's confidence in their ability to perform interventions such as exercises, and barrier self-efficacy is subjects confidence in their ability to overcome barriers to interventions. We will promote task and barrier self-efficacy through subject education, goal setting, reducing barriers, and by providing graphic feedback on goal achievements.

Feedback sheets will be provided to subjects to demonstrate progress over time in adherence to interventions, 1RM measures, weight loads for exercises, and BMD. Scripts will be provided for assisting with goal-setting and reducing barriers to promote standardization across sites. Strategies for reducing barriers to adherence to exercises will be tailored to subjects based on their scores on the Barriers Interference instrument.

6.4 Study Schedule

6.4.1 Prescreening

Potential subjects will be asked to respond to questions on the screening criteria form and Physical Activity Readiness Questionnaire (PARQ) either over the phone or electronically via our study website (see Form 1. Calendar Card Instructions *Form 13. Prescreening Questionnaire.Web_Revised*; *Form 14. Prescreening Qurestionnaire.Verbal_Revised* see *Protocol 20. Prescreening script*). Use *Protocol 21. Prescreening Procedure* to guide this process. If potential subjects meet initial inclusion criteria, they will be mailed a packet of information including: current consent forms*, Form 15. One Page Study Summary_3 , Form 16. What to Expect at your DXA*, *Form 17. Directions to CUMC* ; for printing purposes

use *Packet 1. Block Scheduled Screening Participant*. Upon review of these forms, the potential subject will be scheduled to meet face to face to complete the Screening Consent Form at either the Creighton Osteoporosis Research Center or at UNMC (see *Protocol 22. Steps to Take Prior to Screening Visit*.

6.4.2 Screening Visit

Reference *Protocol 23. Block Screening Meeting* and section below to conduct visit.

To print the forms needed for completion of a screening visit, print *Packet 2. Screening Visit*.

1. Participant arrives or ORC and is directed to waiting room for HOPS study.

2. Immediately upon arrival, look in Screening Binder to identify the individual's ID# and assigned RPC. Mark the participant's folder and *Form 18. Screening Visit Checklist* with ID#, and use highlighter to mark folder tab with assigned RPC's color.

3. Step 1: Completion of Screening Consent
    a. RPC or Investigator greets the participant and reviews the consent form according to screening checklist and protocol (see *Form 19. Screening Consent*; *see Form 18. Screening Visit Checklist*)
    b. Screener signs Screening Consent form indicating informed consent. RPC or Investigator will sign as well.
        i. If participant decides they do not want to participate they are thanked for their time and may leave.

4. Step 2: DXA
    a. HOPS personnel will walk participant down to ORC and let staff know that the participant is ready for their DXA.
    b. Hand *Form 18. Screening Visit Checklist* to participant or staff member. ORC staff will gather height, weight, and waist circumference while the participant is in the ORC completing their DXA and they will record this data on our Checklist.
    c. ORC personnel will complete DXA scan and record total Hip and lumber spine BMD, T-scores.
    d. While participant is completing DXA, double check that all pages of the consent have been initialed (including signature page and last page!) and make a photocopy using the copy machine in the ORC.
        i. We keep the original document. Place the copy in a folder for the participant.
    e. After the DXA, the ORC personnel will direct participant back to the HOPS waiting room.
    f. Once results of DXA are generated ORC personnel will bring results of DXA to HOPS personnel
        i. ORC will provide an original and a copy. Place the copy in the participant's folder and the original in our folder.
5. Step 3: Questionnaires
    a. Whiel the participant is completing the DXA, personnel should open RedCap on the Ipad and assign an ID# according to the *Protocol 24. RedCap Data Entry*
    b. After returning from their DXA, the participant will complete the following questionnaires in RedCap according to the protocol on data entry: *Form 20.*

Osteoporosis Knowledge Test Revised (*must be 1st questionnaire), *Form 21. Demographic Profile , Form 22. FRAX, Form 23. Screening Participants Contact Information Form*_Revised *, Form 24. Human Activity Profile Test (HAP)* and *Form 25. International Physical Activity Questionnaire (IPAQ)*(see *Protocol 25. Administering Osteo Knowledge Test* ; *Protocol 26. Administering FRAX*;*Protocol 27. Administering HAP Questionnaire*; *Protocol 28. Administering IPAQ*

6. Step 4: Reporting DXA Results
    a. Using the *Form 26. Bone Mineral Density Report*, report DXA results to participant.
        i. *If DXA results indicate that the participant has either normal bone density, or that they are osteoporotic*, inform participant that they do not qualify for HOPS
            E. Provide *Form 27. Calcium FAQ*, *Form 28. Vitamin D FAQ*, and *Form 29. Osteoporosis Pamphlet*
            F. If the screener is osteoporotic, HOPS personnel can refer them to a provider for follow up using the *Protocol 29. Referral for Osteoporotic Screeners*.
            G. Provide a flyer or two and ask participant to help spread the word about HOPS to friends and family.
            H. The participant is now finished and may leave.
    b. *If the DXA shows that she has low bone mass (T score between-1 and -2.49), but not yet osteoporosis* (T score < -2.5), the screening subject will be informed that they qualify for the next stage of screening, which includes a blood draw and blood pressure check.
    c. Confirm that screener wants to proceed with the next stage of screening and complete tasks outlined in #7: Step 5, immediately below.
7. Step 5: Blood Draw, BP, and concluding visit:
    a. *If the screener needs to have their blood drawn at the CRC*:
        i. Take blood pressure using *Protocol 30. Checking Resting Blood Pressure* as a guide. Record results on Checklist.
        ii. Discuss an approximate date/time for blood draw so that we know when to expect communication from the CRC.
        iii. Hand them the following forms: *Form 30. CRC Qualification*, *Form 31. CRC Directions with Map*, *Form 32. Further Questions Contact Sheet_Revised* and *Form 29. Osteoporosis Pamphlet*
        iv. Inform participant that we will contact them once we receive the results of their lab work, and at that point, will send a letter to their provider regarding participation in HOPS (see *Form 33. Provider Permission Letter_4*).
        v. Allow participant to leave.
        vi. HOPS personnel should proceed with ordering blood draw by following the appropriate scenario in *Protocol 31. Ordering Blood Draw*
    b. *If the screener has blood drawn on site at the Creighton ORC*:
        i. Take blood pressure using *Protocol 30. Checking Resting Blood Pressure* as a guide. Record results on Checklist.
        ii. Blood draw performed by either Meghan or Ashlee
            E. Meghan and Ashlee are trained to perform phlebotomy and transport specimens, and will follow *Protocol 32. Blood Draw Procedure*, and *Protocol 33. Blood Transportation Protocol*, when performing venipuncture, labeling tubes, and transporting back to the TNMC lab

iii. If participant has questions or concerns about participation in HOPS, provide the *Form 32. Further Questions Contact Sheet_Revised* and *Form 29. Osteoporosis Pamphlet*, and advise that they contact one of the PIs before their enrollment visit
iv. Inform participant that we will contact them once we receive the results of their lab work, and at that point, will send a letter to their provider regarding participation in HOPS (see *Form 33. Provider Permission Letter_4*).

6.4.3 After Screening Visit

If the screener was not qualified, follow the *Protocol 34. Steps to Take After Screening Visit* to complete follow up paperwork.

If the screener has qualified, the following tasks need completed after the screening consent visit:

1. An order for analysis of the sample will need to be placed in One Chart immediately after the screening visit (or during screening consent visit, if personnel are able to remote in to their desktop). Use *Protocol 35. Ordering Blood Tests in One Chart and Enrolling Participant*. ***An order needs to be placed before any specimens are taken to the lab**.
2. HOPS personnel will take one SST (gold top), one PST (green top), and one purple top tube to the TNMC lab. Personnel will keep one SST (gold top) tube and take it up to the lab to centrifuge and aliquot for storage (see *Protocol 36. Blood Handling Procedure* and *Protocol 37. Serum NTx and Alkphase B Aliquot and Storage*).
    a. The following analyses will be performed using screening participants' blood sample: CBC, serum vitamin D, serum calcium, serum creatinine, parathyroid hormone (PTH), follicle-stimulating hormone (FSH) if needed, and subjects diagnosed with a thyroid condition will also have a Thyroid Stimulating Hormone (TSH) test.
    b. At a later date, we will perform analysis of AlkphaseB, Serum NTx, and other soluble factors that may impact bone health (TBD), using the serum from the SST tube stored in Dr. Bilek's -80 freezer.
3. Immediately following this, or on the next business day, HOPS personnel should follow *Protocol 34. Steps to Take After Screening Visit* to complete and/or initiate the remaining items that need completed for screening purposes, including verifying RedCap data, checking lab results, calculating FRAX, etc.
4. If screening subjects remain eligible to participate after undergoing the steps listed above, study personnel will contact the individual's health care provider to request permission for the screening subject to participate in the Heartland Osteoporosis Prevention study (see *Form 33. Provider Permission Letter_4*; see *Protocol 38. Sending Provider Permission Letter*)
5. If permission is granted by the health care provider, the screening subject will be invited to enroll in the main study. The RPC schedules the participant for a time to come go to the ORC to fill out their main study consent, their PQCT, baseline questionnaires, and baseline education.

6.4.4 Enrollment/Baseline

To print the forms needed for an enrollment visit, see *Packet 3. Enrollment Visit Forms*. All other forms needed for this visit are in RedCap. Checklists for this visit are printed and available at the ORC.

1. Complete process of informed consent to the Main Study (see *Form 34. Main Study Consent*; see *Protocol 39. Main Study Consent Guidelines for Completion*.)
2. Randomization: Open the next envelope (envelope on the "top" of the pile located in desk in HOPS office at ORC) and read treatment group out loud.
3. Select the appropriate checklist (see *Form 35. Enrollment Checklist Exercise*, *Form 36. Enrollment Checklist Control*, *Form 37. Enrollment Checklist Risedronate*)
4. Participant will complete *Form 43. NOF Calcium Intake Estimate_Revised* using paper and pencil (see *Protocol 40. NOF Calcium Intake Calculator*)
5. Walk the participant down to the ORC, where they will complete the PQCT. Leave study Checklist with the participant, so that the ORC personnel can initial that the Pqct has been completed. This scan takes approximately 5 minutes.
6. During pQCT:
    1. Open RedCap complete the ID# assignment using *Protocol 24. RedCap Data Entry* (see also *Packet 4. Control Group_All Enrollment Forms*, *Packet 5. Risedronate Group_All Enrollment Forms*, *Packet 6. Exercise Group_All Enrollment Forms*, if you are using hard copy questionnaires).
    2. Locate appropriate Participant Manual (see *Packet 7. Control Group_Participant Manual*, *Packet 8. Risedronate Group_Participant Manual*, *Packet 9. Exercise Group_Participant Manual*). These are located in the ORC, although personnel will need to print copies of these periodically.

Control Group Protocol:

1. Participant Manual will contain the following:
    a. *Form 15. One Page Study Summary_3*
    b. *Form 38. What is Osteoporosis*
    c. *Form 39. Exercise and Your Bones*
    d. *Form 40. Instructions for Calcium and Vitamin D*
    e. *Form 1. Calendar Card Instructions*
    f. *Form 41. Lexicomp Online Patient Education Cholecalciferol*
    g. *Form 42. Lexicomp Online Patient Education Calcium Citrate*
2. Participant will complete the *Form 44. Health History Form* in RedCap
3. Research Project coordinator will educate participant on CaD referencing *Form 45. Instructions for Calcium and Vitamin D Usage* and using *Protocol 42. Administering Edu CaD* as a guide.
4. Participant will complete the *Form 46. Goal Setting CaD form*, *Form 47. Task & Barrier Calcium* and *Form 48. Task & Barrier VitD* form in RedCap
5. RPC will prescribe calcium and vitamin D on the *Form 49. Calcium and Vitamin D Prescription Sheet* using *Protocol 41. Prescribing Calcium and Vitamin D*. RPC will educate participant on usage of the cards using *Form 1. Calendar Card Instructions* document.
6. Participants to be educated on mail back procedure and given SASE for convenience.

Risedronate Group:

1. Participant Manual will contain the same documents as the Participant Manual Control plus the following:
    a. *Form 50. Instructions for Taking Your Risedronate*
    b. *Form 51. Lexicomp Online Patient Education Risedronate*
7. Participant will complete *Form 43. NOF Calcium Intake Estimate_Revised* using paper and pencil (see *Protocol 40. NOF Calcium Intake Calculator*)
8. Participant will complete the Health History Form in RedCap
2. Research Project coordinator will educate participant on CaD using *Form 45. Instructions for Calcium and Vitamin D Usage* as a guide (see *Protocol 42. Administering Edu CaD*)
3. RPC will educate participant on Risedronate using *Form 50. Instructions for Taking Your Risedronate* as a guide (see *Protocol 43. Administering Edu Risedronate*).
4. Participant will complete the *Form 46. Goal Setting CaD form*, *Form 52. Goal Setting Risedronate* form, *Form 47. Task & Barrier Calcium* form, *Form 48. Task & Barrier VitD* form, and *Form 53. Task & Barrier Risedronate* form in RedCap
5. RPC will prescribe calcium and vitamin D using forms and protocols referenced under "Control Group Protocol", #6.
6. Participants to be educated on mail back procedure and given SASE for convenience

Exercise Group Protocol:

1. Participant Manual will contain the same documents as the Participant Manual Control plus the following:
    a. *Form 54. YMCA Membership Application*
    b. *Form 10. YMCA Contact Sheet for Participants_Version 3*
2. Participant will complete *Form 43. NOF Calcium Intake Estimate_Revised* using paper and pencil (see *Protocol 40. NOF Calcium Intake Calculator*)
3. Participant will complete the *Form 44. Health History Form* in RedCap
4. Research Project coordinator will educate participant on CaD using *Form 45. Instructions for Calcium and Vitamin D Usage* as a guide (see *Protocol 42. Administering Edu CaD)*
5. Participant will complete the *Form 46. Goal Setting CaD form, Form 47. Task & Barrier Calcium*and *Form 48. Task & Barrier VitD* form in RedCap
6. Participant will complete the *Form 54. YMCA Membership Application* and be introduced to Exercise program. Use *Protocol 44. Steps to Take After Randomization to Exercise Group* as a guide.
7. RPC will prescribe calcium and vitamin D using forms and protocols referenced under "Control Group Protocol", #6.
8. Participants to be educated on mail back procedure and given SASE for convenience.

Note: During week 2, RPC will complete the following instruments with the participant: 1. *Form 55. Goal Setting Exercise*, 2. *Form 56. Task and Barrier Exercise*, and 3. *Form 57. Barriers Interference Instrument*, and the following educational materials: 1. *Form 58. Reminder List for Exercises*, 2. *Form 59. Signs and Symptoms*, 3. *Form 60. Sore vs. Pain*, 4. *Form 61. Know the Facts About High BP*, 5. *Form 62. HOPS Posture*

7. RPC will fill out *Form 63. Payment Info Form*. If personnel ID is unknown, ask participant to send via email or verify over the phone.
8. RPC will give all participants a chance to ask any questions and ensure they understand the process of the study. RPC will remind participant that they will contact the participant in two weeks.

6.4.5 After Enrollment Visit

Follow the steps listed in *Protocol 45. Steps to Take After Enrollment Visit* . This will include issuing the participant's first payment. Use *Protocol 46. Issuing Participant Payment Request* , as a guide.

If the participant was assigned to the Exercise group, make sure that the items outlined in *Protocol 44. Steps to Take After Randomization to Exercise Group* have been addressed.

If the participant was randomized to the Risedronate group, follow the steps listed in *Protocol 47. Acquiring Risedronate Rx* , to attain a risedronate prescription for the participant.

6.4.6 Intermediate Visits

Subjects will have follow up contact at 2 weeks, 3M, 6M, and 12M. Additional contact will be made between exercise participants and Melissa, the RET. Additional contact will occur between RPCs and participants as needed. If at any time during enrollment, a participant indicates that they have suffered a fracture, the participant will be asked to complete the *Form 64. Fractures Documentation_Revised*, and the participant's provider will determine whether continuation in the study is appropriate.

See *Protocol 1.Timeline for Data Collection* for details.

7 STUDY PROCEDURES /EVALUATIONS

7.1 Study Procedures

See *Protocol 1.Timeline for Data Collection* for details.

Protocol 48. Data Collection_Control Group, *Protocol 49. Data Collection_Risedronate Group* ,*Protocol 50. Data Collection_Exercise Group* for detailed data collection timelines according to treatment group.

7.2 Laboratory Procedures/Evaluations

7.2.1 Clinical Laboratory Evaluations

Screening blood tests will include:

- CBC
- Serum vitamin D
- Serum calcium
- Serum creatinine
- Parathyroid hormone
- Follicle-stimulating hormone (if applicable)
- Thyroid stimulating hormone (if applicable)
- Additional serum drawn at screening will be stored and used for baseline analysis of Alkphase B and Serum NTx (markers of bone turnover) and other factors that may affect bone health

Blood tests performed at 6 months:

- Serum vitamin D
- Alkphase B
- Serum NTx

Blood tests performed at 12 months:

- Alkphase B
- Serum NTx

7.2.2 Special Assays or Procedures

- Dual energy x-ray absorptiometry (DXA) at screening(baseline), 6M, 12M
    - Hip Structural Analysis at screening (baseline), 6M, 12M
    - Trabecular Bone Score at screening, 6M, 12M
- Peripheral quantitative computed tomography (pQCT) at baseline, 6M, 12M
- Estimated 1 repetition maximum (1 RM) at 2 weeks, 6M

7.2.3 Specimen Preparation, Handling, and Storage

Blood draws will be performed at either TNMC Clinical Research Center or at the Creighton Osteoporosis Research Center depending on subject availability and preference. Personnel will follow appropriate protocols for venipuncture and transportation of specimens (see *Protocol 32. Blood Draw Procedure* , and *Protocol 33. Blood Transportation Protocol*). As indicated in *Protocol 33. Blood Transportation*

Protocol , some specimens will be stored in Dr. Bilek's lab, while others will be analyzed by the TNMC laboratory. For specimens to be aliquoted and stored in Dr. Bilek's lab and freezer space, *use Protocol 36. Blood Handling Procedure* and *Protocol 37. Serum NTx and Alkphase B Aliquot and Storage* as a guide.

8 ASSESSMENT OF SAFETY

8.1.1 Data

The location of the server is a password protected secured campus UNMC RedCap database server.This server is accessible from the external network, so researchers can design their surveys and provide a link to complete the survey that will work from any Internet-connected device, including mobile devices. This has a secure HTTPS connection. (Please see attached file named: ***RedCapServerInfoIRB.Docx***, for more detailed information on the servers and firewall).

Best practices are followed by UNMC IT where the web server and database server are two separate servers and both the web server and database server are securely located behind a firewall. (Please see attached file named:***RedCapServerInfoIRB.Docx***,for more detailed information.).

Exercise logs used by subjects to document their exercises will be stored at individual Y's and then transported by study personnel every 4 weeks for entry into the online data base . On-site ET coordinators at Y's will monitor subject's adherence to exercises by examining subject exercise logs every 2 weeks during the study. Exercise logs must be stored at the Y's because they are used by subjects to document their exercises and by on-site ET coordinators to monitor fidelity of the exercise intervention. Hard copies of data will be kept locked in a file cabinet in the locked office of the study coordinator or the locked office of one of the PIs. Data will be transported in a locked briefcase.

Research data will be linked to subjects by ID code number only. Each subject will be assigned an ID code for use on all study materials. The only link between a subject's name and ID code will be the consent form. A copy of the consent form will be kept in the PI's research office in a locked file separate from other study materials.
As specified by the NIH, subject identifiers will be maintained for 7 years after the study is completed. Funding for the study is requested for 5 years, and study data will be kept for an additional 7 years. All electronic data will be destroyed with the assistance of the ITS and in accordance with UNMC Computer Use and Electronic Information Security Policy N0. 6051

8.1.2 Adverse Events

If a subject is injured or has a medical problem as a direct result of being in this study, the subject has been instructed to immediately contact a member of the study personnel listed at the end of the consent form.

The institution has no plans to pay for any required treatment or provide other compensation. If the subject has insurance, the insurance company may or may not pay the costs of medical treatment. If the subject does not have insurance, or if the insurance company refuses to pay, the subject will be expected to pay for the medical treatment. The subject will be informed that by participating in this research study, she has not given up any of her legal ri

STUDY OVERSIGHT

The conduct and scientific integrity of this proposed clinical trial will be monitored by a Data and Safety Monitoring Committee (DSMC), comprised of the following persons: Joseph Norman, PT, PhD, Professor, Divison of Physical Therapy Education; Jane Meza, PhD, Professor College of Public Health Biostatistics; M. Patricia Leuschen, Professor Emeritus, School of Allied Health Professions; and Bernice Yates, RN, PhD, Professor, College of Nursing. The DSMC will audit the implementation of the protocol beginning 6 months after the start of subject accrual. Since this trial is greater than minimal risk, it will be audited every 6 months. Each report will include monitoring of: compliance with informed consent and eligibility requirements, recruitment plan according to protocol, follow-up data collection according to protocol, expected and actual accrual, protocol violations, and patient withdrawals from the study. Per university policy, all serious adverse events (AE) will be reported to the UNMC IRB, the NIH, and to the DSM Committee within two business days after the investigators have been notified of the AE. The investigators will prepare a summarized report of these above-listed items and submit this report to the DSMC, with access to raw data if needed. A report from the DSMC audit will be sent to the investigators, the UNMC IRB, and NINR-NIH.

The conduct and scientific integrity of this proposed clinical trial will be monitored by a Data and Safety Monitoring Committee (DSMC), comprised of the following persons: Joseph Norman, PT, PhD, Professor, Divison of Physical Therapy Education; Jane Meza, PhD, Professor College of Public Health Biostatistics; M. Patricia Leuschen, Professor Emeritus, School of Allied Health Professions;; and Bernice Yates, RN, PhD, Professor, College of Nursing.

9 CLINICAL SITE MONITORING

The Research Project Coordinators (RPCs) and the Research Exercise Trainer (RET) (under the direction of the Co-PIs Dr Waltman and Dr Bilek) will conduct audits to monitor compliance with intervention and testing protocols and to monitor unanticipated problems involving risks to the subjects at random times and at least every 3 months of the study. Reports of violations will be submitted to the IRB as required.The conduct and scientific integrity of this proposed clinical trial will also be monitored by a Data and Safety Monitoring Committee (DSMC). The DSMC will audit the implementation of the protocol beginning 6 months after the start of subject accrual. Since this trial is greater than minimal risk, it will be audited every 6 months. Each report will include monitoring of: compliance with informed consent and eligibility requirements, recruitment plan according to protocol, follow-up data collection according to protocol, expected and actual accrual, protocol violations, and patient withdrawals from the study. Per university policy, all serious adverse events (AE) will be reported to the UNMC IRB, the NIH, and to the DSM Committee within two business days after the investigators have been notified of the AE. The investigators will prepare a summarized report of these above-listed items and submit this report to the DSMC, with access to raw data if needed. A report from the DSMC audit will be sent to the investigators, the UNMC IRB, and NINR-NIH.

The same auditing plan will be used for external study sites involved in the study, including all "Y" facilities and the Creighton University Research Center. As described previously, audits will be conducted by the RPCs and RET (under the direction of the Co-PIs Dr Waltman and Dr Bilek) and also by the DSMC.

10 DATA ENTRY/STATISTICAL CONSIDERATIONS

10.1 Data Entry

As indicated in Section 9.1.1, HOPS data will be entered and stored on a password protected, secured campus UNMC RedCAP database server. The server is accessible from an external network, therefore the database offers the capability to enter data off site. We will be utilizing Ipads to enter participant data offsite, and data will be entered by both HOPS personnel and participants. Styluses and keyboards have been purchased to increase ease of entry and to minimize error. Additionally, limitations have been set in RedCAP so that the database will notify the user any time a value outside of the normal range is submitted, allowing the user an opportunity to correct an error. In order to avoid any risk of violations of confidentiality, participants will have limited access to RedCAP, and will therefore, only be able to view the necessary forms.

See *Protocol 24. RedCap Data Entry* for detailed directions on data entry and usage of the RedCAP database.

10.2 Sample Size Considerations

A power analysis was conducted for the primary aim of the study since it involves the most complex analysis. Hypothesis 1a states that at 12 months, there will be significantly greater improvements in BSI at the 4% tibial site in subjects in the exercise group compared to subjects in the control or risedronate groups. Power for the repeated measures analysis of variance (RM-ANOVA) was determined using G*Power3.1.5. A within-between interaction will be the primary test of significance (time*group interaction). It is assumed that the exercise group will have significantly greater improvements in BSI than either the control or risedronate groups. Two groups were assumed for the purposes of the power analysis because the control and risedronate groups will be compared to the exercise group separately. The total sample size will then be the number determined plus one half to populate the three groups. We investigated effect size evidence from similar studies and a variety of effect sizes was observed. However, effect sizes were not reported in the studies that were deemed most similar to the planned study. This study compares an exercise group to control and risedronate groups, which is unique so a large expected effect size could not be assumed without further evidence.
Therefore, a small effect size was assumed for this power analysis (f=.10; Cohen 1992). Assuming a significance level of .05, 3 time points, and an estimate of .5 for the correlation between time points, 246 participants (82 per group) would be needed to have 80% power.

10.3 Final Analysis Plan

Aim 1 hypotheses will be tested via RM-ANOVA models. Bone strength index at the tibia and bone mass distribution at the hip, the dependent variables of interest, will be measured at 6-month intervals (0, 6, and 12 months). A significant time*group interaction would indicate that the two groups being compared in each model have significantly different changes in bone structure over 12 months. Huynh-Feldt corrected F-tests will be used in order to account for any possible violation of sphericity. It is hypothesized that the exercise group will have significantly greater improvements than the control or risedronate groups. Up to 20% attrition may be expected over the course of the study, but we expect it

to be less due to the use of cognitive behavioral strategies by Research Project Coordinators (RPC), the Research Exercise Trainer (RET), and ETs to promote exercise adherence and retention in the study. The method of handling missing data is not likely to have an effect with small amounts of missing data. However, If there is a higher than expected attrition rate, a maximum likelihood estimation method (e.g. mixed models) will be used instead of RM-ANOVA in order to utilize all available data and not delete cases in a listwise manner.

Hypothesis 2a compares the groups changes in BMD and will also be analyzed using RM-ANOVA. Hypothesis 2b also involves BMD, but assesses the proportions of preservation of BMD in each group. It is expected that at least 80% of subjects in both the exercise+ and risedronate+ groups will have preserved BMD at the three skeletal sites, and that the control/CaD group will have a significantly lower proportion of participants preserving BMD over 12 months. In order to classify individuals into preserved vs. declined groups, change in BMD over 12 months will be compared to the least significant difference as defined by the Hologic DXA manufacturer for each respective skeletal site. Differences of proportion of preservation across groups will be assessed via chi-square tests, which would indicate if preservation of BMD was significantly different across groups. Aim 3 investigates the changes in bone formation and resorption over 12 months also using repeated-measures ANOVA. Alkphase B and Serum NTx will be measured at baseline, 6, and 12 months.

The relationships of interest in Aim 4 will be explored by assessing the correlations between percentage of sessions attended, percentage of risedronate pills taken, and 12-month changes in bone structure at the tibia and hip. Assuming the variables are normally distributed, Pearson correlations will be used. Spearman rank correlations will be used if any of the variables are found to be non-normal.

11 ETHICS/PROTECTION OF HUMAN SUBJECTS

See IRB Application

DATA HANDLING AND RECORD KEEPING

See IRB Application

12 LITERATURE REFERENCES

APPENDICES

APPENDIX B: PROTOCOLS

Protocol 1.Timeline for Data Collection

Protocol 2. CaD Delivery_RPC Responsibilities

Protocol 3. Risedronate Delivery_RPC Responsibilities

Protocol 4. First Exercise Session Explanation and Documentation

Protocol 5. Estimating 1RM

Protocol 6. YET HOPS Exercise Schedule

Protocol 7. Progression and Increase Parameters for Exercise

Protocol 8. Impact Jogging

Protocol 9. Graphic Feedback

Protocol 10. Exercise Trainer Oversight Schedule_Revised

Protocol 11.Storing Exercise Docs at YMCAs

Protocol 12.Addressing Missing Exercise Session, Adherence

Protocol 13. Addressing Continued Exercise Non-Compliance

Protocol 14. Exercise Group_Addressing Withdrawn or Off-Protocol Participants

Protocol 15. Exercise Group_Addressing Problems on YET Doc Form

Protocol 16. Using Barrier Intervention Strategies

Protocol 17. RET Protocol for YMCA Exercise Sessions by Visit

Protocol 18. Scheduling YET Visits

Protocol 19. Storing Scanned-In Exercise Documents

Protocol 20. Prescreening script

Protocol 21. Prescreening Procedure

Protocol 22. Steps to Take Prior to Screening Visit

Protocol 23. Block Screening Meeting

Protocol 24. RedCap Data Entry

Protocol 25. Administering Osteo Knowledge Test

Protocol 26. Administering FRAX

Protocol 27. Administering HAP Questionnaire

Protocol 28. Administering IPAQ

Protocol 29. Referral for Osteoporotic Screeners

Protocol 30. Checking Resting Blood Pressure

Protocol 31. Ordering Blood Draw

Protocol 32. Blood Draw Procedure

Protocol 33. Blood Transportation Protocol

Protocol 34. Steps to Take After Screening Visit

Protocol 35. Ordering Blood Tests in One Chart and Enrolling Participant

Protocol 36. Blood Handling Procedure

Protocol 37. Serum NTx and Alkphase B Aliquot and Storage

Protocol 38. Sending Provider Permission Letter

Protocol 39. Main Study Consent Guidelines for Completion

Protocol 40. NOF Calcium Intake Calculator

Protocol 41. Prescribing Calcium and Vitamin D

Protocol 42. Administering Edu CaD

Protocol 43. Administering Edu Risedronate

Protocol 44. Steps to Take After Randomization to Exercise Group

Protocol 45. Steps to Take After Enrollment Visit

Protocol 46. Issuing Participant Payment Request

Protocol 47. Acquiring Risedronate Rx

Protocol 48. Data Collection_Control Group

Protocol 49. Data Collection_Risedronate Group

Protocol 50. Data Collection_Exercise Group

APPENDIX B: FORMS

Form 1. Calendar Card Instructions

Form 2. Blank Calendar

Form 3. HOPS Exercise Booklet_Revised

Form 4. Starting Load Values Based Upon Body Weight

Form 5. Borg RPE scale

Form 6. YET HOPS Exercise Schedule

Form 7. Progression and Increase Parameters for Exercise

Form 8. Exercise Log_Revised

Form 9. Exercise Trainer Oversight schedule revised

Form 10. YMCA Contact Sheet for Participants_Version 3

Form 11. Availability of YETs

Form 12. YET Documentation Form

Form 13. Prescreening Questionnaire.Web_Revised

Form 14. Prescreening Qurestionnaire.Verbal_Revised

Form 15. One Page Study Summary_3

Form 16. What to Expect at your DXA

Form 17. Directions to CUMC

Form 18. Screening Visit Checklist

Form 19. Screening Consent

Form 20. Osteoporosis Knowledge Test Revised

Form 21. Demographic Profile

Form 22. FRAX

Form 23. Screening Participants Contact Information Form_Revised

Form 24. Human Activity Profile Test (HAP)

Form 25. International Physical Activity Questionnaire (IPAQ)

Form 26. Bone Mineral Density Report

Form 27. Calcium FAQ

Form 28. Vitamin D FAQ

Form 29. Osteoporosis Pamphlet

Form 30. CRC Qualification

Form 31. CRC Directions with Map

Form 32. Further Questions Contact Sheet_Revised

Form 33. Provider Permission Letter_4

Form 34. Main Study Consent

Form 35. Enrollment Checklist Exercise

Form 36. Enrollment Checklist Control

Form 37. Enrollment Checklist Risedronate

Form 38. What is Osteoporosis

Form 39. Exercise and Your Bones

Form 40. Instructions for Calcium and Vitamin D

Form 41. Lexicomp Online Patient Education Cholecalciferol

Form 42. Lexicomp Online Patient Education Calcium Citrate

Form 43. NOF Calcium Intake Estimate_Revised

Form 44. Health History Form

Form 45. Instructions for Calcium and Vitamin D Usage

Form 46. Goal Setting CaD form

Form 47. Task & Barrier Calcium

Form 48. Task & Barrier VitD

Form 49. Calcium and Vitamin D Prescription Sheet

Form 50. Instructions for Taking Your Risedronate

Form 51. Lexicomp Online Patient Education Risedronate

Form 52. Goal Setting Risedronate

Form 53. Task & Barrier Risedronate

Form 54. YMCA Membership Application

Form 55. Goal Setting Exercise

Form 56. Task and Barrier Exercise

Form 57. Barriers Interference Instrument

Form 58. Reminder List for Exercises

Form 59. Signs and Symptoms

Form 60. Sore vs. Pain

Form 61. Know the Facts About High BP

Form 62. HOPS Posture

Form 63. Payment Info Form

Form 64. Fractures Documentation_Revised

APPENDIX C: PACKETS

Packet 1. Block Scheduled Screening Participant

Packet 2. Screening Visit Forms

Packet 3. Enrollment Visit Forms

Packet 4. Control Group_All Enrollment Forms

Packet 5. Risedronate Group_All Enrollment Forms

Packet 6. Exercise Group_All Enrollment Forms

Packet 7. Control Group_Participant Manual

Packet 8. Risedronate Group_Participant Manual

Packet 9. Exercise Group_Participant Manual