

STUDY PROTOCOL

Title: Micromechanical Modeling Using Low Magnitude Mechanical Stimulation (LMMS)

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Introduction

This double-blinded, translational, human subject study will test the hypothesis that postmenopausal women, subjected to a daily 10-minute treatment of LMMS (low magnitude mechanical stimulation) for one year, will show an improvement in trabecular and cortical stiffness and failure strength at the tibia, along with a reduction in vertebral marrow adiposity relative to their placebo-treated peers. The intervention and measurement protocols pose minimal risk to participants.

Abstract

We propose to evaluate the hypothesis that LMMS applied to postmenopausal women ages 45-65 improves the bone's mechanical integrity while lowering marrow adiposity. Specific Aims are: 1) We will optimize an integrated imaging protocol for high-resolution structural MR imaging of the distal tibia and spectroscopic imaging-based quantification of bone marrow composition in the lumbar vertebrae; 2) We will further develop and validate micro-finite-element (FE) analysis for quantitative assessment of trabecular and cortical bone stiffness and failure load from high-resolution MR images of the distal tibia, and 3) We will apply the methodology of Aims 1 and 2 in a double-blinded, randomized, placebo-controlled study to a cohort of 64 healthy postmenopausal women in the age range of 45-65 years, studied at baseline and 12 months after having been subjected to 10 minutes daily of either 30 Hz/0.3g stimulation or placebo treatment, monitored rigorously via electronic feedback.

Overall objectives

We hypothesize that relative to placebo, LMMS treatment will result in: 1) increased trabecular and cortical stiffness and failure strength assessed at the distal tibia by MR image-based FE modeling; 2) increased BMD at the two peripheral sites measured by pQCT, and DXA of the spine and hip, and 3) reduced vertebral marrow adiposity, which will be reciprocally related to measures of BMD and strength.

Primary outcome variable(s)

Increased trabecular and cortical stiffness and failure strength, assessed at the distal tibia by MR image-based FE modeling.

Secondary outcome variable(s)

Increased BMD at the two peripheral sites measured by pQCT and DXA of the spine and hip.

Background

Weight bearing exercise has an osteogenic effect by reducing bone resorption and enhancing bone formation. During the past several years a number of articles have appeared demonstrating that low magnitude mechanical stimulation (LMMS) is osteogenic in animals and also in humans. The mechanobiology underlying these phenomena is beginning to emerge in terms of expression of genes stimulated by the action of the vibrations to which osteocytes are subjected. If successful, LMMS treatment, a non-pharmacologic intervention, could prevent bone loss and potentially stimulate bone formation resulting in increased bone strength and reduced fracture susceptibility in subjects at risk of developing osteoporosis. The proposed project focuses directly on measures of strength by evaluating the therapeutic response in terms of magnetic resonance (MR) image-based micro finite-element (FE) assessment of bone stiffness and failure strength, along with quantifying treatment-induced changes in marrow adiposity, as part of a single, integrated examination, conducted at baseline and 12 months of treatment in a double-blinded, randomized, placebo-controlled study of postmenopausal women. Special consideration will be given to compliance, which will be enhanced by an electronic feedback system.

Study phase

Phase II

Study design

Double blinded, randomized, placebo-controlled.

Study duration

Estimated length of time for enrollment: 2 years

Length of time of subject participation: 1 year

Resources necessary for human research protection

All research staff involved with this study are experienced performing MRI studies of this type and all have completed the required training in human subjects research protection. The DXA and pQCT studies will take place in The Nutrition and Growth Lab at Children's Hospital of Philadelphia. The Nutrition and Growth Lab is used for many of the studies involving DXA and pQCT at the University of Pennsylvania. The MRI research facility at the University of Pennsylvania has dedicated scanners devoted to various research projects. Subjects will be recruited from a database of previous study participants as well as with outreach efforts to the University and general community via advertisements, letters and notices.

Target population

Post-menopausal female subjects ages 45-65 years who have a history of amenorrhea for a minimum of 24 months and a serum FSH of 25 or greater.

Subjects randomized by Penn researchers

83 (to reach final sample of 64 completers)

Subjects enrolled by collaborating researchers

0

Accrual

Subjects will be recruited from a database of previous study participants as well as with outreach efforts to the university and general community via advertisements, letters and notices. These methods have been successful in prior clinical trials.

Key inclusion criteria

Females, ages 45-65 years in post-menopause, as defined by a history of amenorrhea for a minimum of 24 months and a serum FSH concentration of 25 mIU/mL and negative pregnancy test

Key exclusion criteria

Current and prior use of medications known to affect bone (e.g. bisphosphonates, calcitonin, selective estrogen receptor modulators, denosumab, diphenylhydantoin, or glucocorticoids) may be considered for exclusion, bone mineral density T score of less than -2.5 and greater than +2, vitamin D level less than 12 ng/ml, BMI of greater than 32, current alcohol or drug abuse (more than 3 alcoholic beverages per day or current use of illicit drugs or prescription medications), uncontrolled or untreated cardiac or pulmonary disease, liver disease (history of hepatitis or ALT or AST greater than 2x ULN), renal disease (history of renal disease or serum creatinine greater than 2x ULN), diabetes, Pacemaker or metallic implants (considered contraindicated to MR scanning).

Vulnerable populations

The following populations are not included in this research study: children, pregnant women, prisoners.

Subject recruitment

Subjects will be recruited from a database of previous study participants as well as with outreach efforts to the university and general community via advertisements, letters and notices. These methods have been successful in prior clinical trials. Additionally, we will use the Penn Clinical Data Warehouse's (Penn Data Store) services.

Study procedures

Screening visit: Subjects will be scheduled to meet with the study coordinator in the Nutrition and Growth Laboratory at Children's Hospital of Philadelphia. The consent form will be reviewed and signed after all

questions are answered. Subjects will provide information regarding medical history and current medications. Inclusion and exclusion criteria will be reviewed. A urine pregnancy test will be performed. Subjects will undergo a DXA of the hip and spine. If total bone mineral density does not indicate osteoporosis (total BMD in hip or spine equal to or less than -2.5.), we will proceed with additional screening. For those who qualify for the study based on BMD, blood will be drawn for a comprehensive metabolic panel, 25(OH)D, HgbA1c, TSH and FSH and the individual will undergo a pQCT of the tibia. If lab results indicate no evidence of bone disease and that the subject is post-menopausal (FSH greater than 25 mIU/mL), a baseline visit will be scheduled.

Baseline visit: Subjects will undergo MRI scans of the tibia and spine taking 60 minutes. It is possible that a subject will need to return for a repeat MRI scan if the initial scan is unsatisfactory due to technical reasons. Subjects will then be randomized by the device manager to receive an active or placebo Juvent device and will be instructed to stand on the device for a 10 minute period daily. To mask the active/placebo status, all devices are equipped with a small speaker that emits an audible tone. All subjects will be provided with a supply of calcium carbonate and vitamin D3 supplementation. We will dispense 1200 mg/day of calcium carbonate and 1000 IU/day of vitamin D3 in combined form (soft gel, two pills daily) to be taken by all subjects throughout the 12 month duration of the trial.

Randomization and blinding: Subjects meeting the entry criteria at the screening visit will be randomly allocated 1:1 to an active LMMS or a placebo device. The subjects will then be assigned a treatment number. Participant's names and study numbers will be kept in a password-protected database separate from other study records. Random numbers will be generated by a random number generator by the unblinded device manager who will maintain a database with even numbers being assigned to treatment and odd numbers to placebo. This database will not be shared with the PI or other members of the study team before completion of the study. The project manager will be responsible for storing the Juvent devices and the device manager will be responsible for dispensing them to the study staff as determined by the randomization number.

Monitoring of adherence: Data stored on the Juvent devices will be collected by the study team during the six month visit and twelve month visit via a serial connector. The study team will be able to monitor the date, time and duration of each use. The study coordinator will contact subjects bi-weekly to discuss adherence and to provide support.

Six-month visits: Subjects will return to the study site with their Juvent devices. The study team will collect study data from the device via a serial connector. The study team will also review medical status, supplement compliance and to record any adverse events. Additional calcium carbonate/vitamin D3 will be provided if needed.

Twelve-month visit (study completion): Subjects will return to the study site with their Juvent devices. The study team will collect study data from the device via a serial connector. Subjects will return for DXA of hip and spine, pQCT of the tibia and MRI of tibia and spine, as well as a review of medical status, supplement compliance and any adverse events.

Adherence to Study Drugs

Supplement Accountability and Handling - Calcium Carbonate and Vitamin D3 Supplementation

We will dispense 1200 mg/day of calcium carbonate and 1000 IU/day of vitamin D3 in combined form (soft gel, two pills daily) to be taken by all subjects throughout the 12 month duration of the trial. Supplements will be purchased by the study project manager. Supplements will be purchased based on availability and price. They will be shipped directly to the Hospital of the University of Pennsylvania. The supplements will be stored in a locked closet in a secured area in the MRI Education center. Only the study coordinator and study project manager will have access to the supplement stock. The dispensing will be conducted by the study coordinator.

At baseline visit each subject will be provided with a six month supply of supplements and asked to take them daily. Subjects will be asked to document any missed supplements by noting this in a journal provided by the study team. As the study coordinator will call each subject bi-weekly to discuss study progress, any concerns or adverse events, subjects will also be asked at this time about supplement compliance. Non-compliant days

will be noted by the study coordinator in the subject's file. At the six month visit subjects will be asked to turn in their supplement bottles. The study coordinator will count and record the amount of pills remaining, if any. All necessary information will be documented on the dispensing and tracking log. Any remaining supplements will be discarded. At the end of this visit the study coordinator will provide each subject with another six month supply of supplements to be taken daily as outlined above. When subjects return for the final 12 month visit they will be asked to turn in their supplement bottles. The study coordinator will count and record the amount of pills remaining, if any. All necessary information will be documented on the dispensing and tracking log. Any remaining supplements will be discarded.

Safety issues

Radiation: This research study involves exposure to radiation from the DXA and pQCT scans and therefore subjects will receive a small radiation dose. This radiation dose is not necessary for medical care and will occur only as a result of participation in the study. At doses much higher than subject will receive, radiation is known to increase the risk of developing cancer after many years. At the doses subject will receive, it is very likely they will see no effects at all.

Blood draw: The blood sampling process infrequently causes pain, bruising, bleeding, vein infection and/or vein clotting at the site, and possible fainting. There is little risk in providing five teaspoons of blood in a healthy individual.

MRI: The known risks associated with MRI are minimal. MRI uses radio waves and a magnetic field to take pictures. The magnet is always on. Some individuals may feel claustrophobic (uncomfortable in small spaces) during the MRI scan or may be disturbed by the sounds of the machine, which are loud and repetitive. Any metal objects on or inside the body may heat up, move and/or not function properly within the scanning room. To minimize any risk from these objects, MRI personnel will screen all subjects. Another risk is that from a metallic object flying through the air toward the magnet and hitting the subject. There are many safety measures in place to reduce this risk, including screening of all persons and materials entering the scanning room. In addition, as the study begins, the door to the room will be closed to minimize the risk of someone accidentally walking into or bringing an object into the magnet room. Some of the pulse sequences and/or RF coils are not FDA approved but are considered to pose no more than minimal risk. It is possible that during the course of the study, the research staff may notice an unexpected finding. Unexpected findings will be considered by the appropriate personnel and the PI will inform the subject if necessary. These possible findings may or may not be significant and may lead to anxiety.

Reproductive risks: Since DXA and pQCT involve radiation, a negative urine pregnancy test will be required before a woman of childbearing potential can participate in this study.

Juvent Vibration Platform: The FDA has designated the risk of the Juvent Vibration Platform as "non-significant".

Subject confidentiality

Subjects will be provided with a study ID, which will consist a unique study number and subject ID (e.g. 9943-001). All patient files will be stored in a locked cabinet in the study coordinator's office. The subject ID will be used for all DXA, p-QCT, and MRI studies.

Subject privacy

HIPPA privacy rules will be observed. Subjects will be interviewed in a private room. All study testing will be conducted in closed areas.

Institutional Review Board procedures

Human research must be reviewed by a convened meeting of the IRB unless the research is determined to be exempt or is eligible for expedited review. The final review category and submission requirements will be determined by the IRB. The work of reviewing submissions is divided among eight IRBs. IRBs 1 through 5 and IRB 7 review general medical research. IRB 8 reviews social and behavioral research. IRB 6 serves

Pennsylvania Hospital. If the protocol requires review by the full IRB at a convened meeting, the PI will be notified of the assignment of the protocol to an appropriate IRB within two days of receipt by the IRB. An expedited review consists of a review of research involving human subjects by the appropriate IRB executive chair or his/her designee. In reviewing the research, the reviewer may exercise all of the authorities of the convened IRB except that the reviewer may not disapprove the research. Additionally, the reviewer may refer the application to the convened IRB for a standard review as warranted.

In general, this assignment will be to the next scheduled meeting of an appropriate IRB (provided that the submission is complete). The IRB will review no more than 25 agenda items at each meeting (including new submissions, continuing reviews, amendments, unanticipated problems posing risks to subjects or others, or previously tabled protocols). Agenda items in excess of 25 will be assigned to the next scheduled meeting of an appropriate IRB.

The IRB application for continuing review must be submitted no later than six weeks prior to the expiration date for convened board review and no later than two weeks for expedited review.

NOTE: No research related activities may occur after the protocol expiration date unless the PI contacts the IRB and the IRB executive chair (or authorized designee) determines that it is in the best interest of subjects to continue during the lapse in IRB approval. Federal regulations require that modifications in approved research, during the period for which approval has already been given, may not be initiated without prior IRB review and approval except where necessary to eliminate apparent immediate hazards to human subjects. Sometimes modifications are noted or recognized after they occur. These changes will be reviewed by the IRB as events that may represent unanticipated problems involving risks to participants or others and to determine whether the change was consistent with ensuring the participants' continued welfare. The IRB categorizes modifications into three types: amendments, deviations, and exceptions.

Consent process

The study coordinator will provide a prospective subject with an explanation of the study in person or by phone (If possible the coordinator will mail or email the consent to the prospective subject). If the subject verbally agrees during the phone screening the study team will then schedule an appointment during which the consent will be reviewed and signed after all questions have been answered. A signed copy of the consent form will be given to the participant. Informed consent documents will be stored in a secured location where the study team only has access to them. If changes are made to the consent or study procedures, participants will be required to re-consent. If the subject decides not to participate, they are free to leave the study at any time. Withdrawal will not interfere with future care.

Analyses

Axial stiffness and failure strength: To estimate the axial stiffness of cortical bone (CB), trabecular bone (TB) and whole bone (WB) section compressive loading will be simulated in the linear elastic regime. Here, 1% axial strain will be applied to the proximal face of the μ FE model while keeping the distal face constrained in the axial direction while assuming frictionless conditions along the transverse directions. The μ FE models will then be solved for all three bone-compartments (CB, TB and WB). Axial stiffness is obtained as the ratio of the stress on the proximal face to the applied strain. Failure strength will be estimated assuming that bone fails when a significant portion (2%) is strained beyond the tissue yield strain chosen as 0.7%. In addition, 3D strain-energy maps will be created from upsampled images and histograms generated.

Vertebral bone marrow adiposity: An average fat volume fraction will be computed for each of the five lumbar vertebrae as " $f = V_f / (V_f + V_w)$ " where V_f and V_w are the voxel volumes of fat and water, each computed as an average of the four central voxels, via Eqs. 1 and 2. Relaxation times for computing saturation factors will be mean values obtained from the data collected under Aim 1 in a sub-group of subjects.

Descriptive statistics: To describe participant's baseline characteristics and study outcome measures at baseline and one-year follow-up, data will be recorded overall and within each treatment group. Baseline characteristics will include distribution of age, race/ethnicity, adherence data and outcome variables. Summary

statistics (standard deviations, medians, and ranges) will be tabulated for all measured variables and their frequencies computed. Graphical methods including stem-and-leaf diagrams and box plots will be used to examine distributions, identify potential influential points, and guide in the choice of transformations if warranted. Baseline measures across the treatment groups will be compared using appropriate 2-sample tests including tests, Wilcoxon rank-sum tests and Fisher's exact tests. All analyses will be conducted using Stata 9.0 and SAS (for analysis of adherence data) with two-sided tests of hypotheses and a p-value < 0.05 indicating significance. Changes in primary and secondary outcomes within patients over the 12-month study period will be calculated as differences within subjects and as % changes.

Outcome analyses: All analyses will be done according to the *intention to treat* principle. The primary endpoint is the change in distal tibia trabecular bone whole-section axial failure strength over the 12-month study interval. The primary hypothesis to be tested is that treatment with the active LMMS device results in greater change in this parameter than treatment with the placebo device over a 12-month period. The secondary hypothesis to be tested is that vertebral marrow adiposity is reduced in the treatment relative to the control subjects. To evaluate the changes from baseline within groups, 2-sided paired t-tests will be performed for both groups. Unpaired t-tests will be used to test the primary and secondary hypotheses that the means of the temporal changes are different between treatment groups. Linear regression models will also be constructed to compare mean within-subject changes between groups. These models will include differences within subjects as the outcome variable, and an indicator variable for treatment group and baseline measurement as the covariates. In this manner we will be able to evaluate whether the treatment effect is associated with baseline values. Further, since the efficacy of LMMS treatment has been shown to critically hinge on adherence, post-hoc analyses will be performed by considering adherence, for example, by excluding data from subjects with the lowest quartile of compliance. Lastly, we will examine the hypothesis that the treatment effect scales with compliance using regression analysis.

Secondary analyses: Other parameters evaluated comprise various measures of stiffness and strength analyzed from the MRI-derived μFE data, as well as structural measures (trabecular parameters of scale and topology at the distal site) and bone densitometry quantities, defined previously. Besides axial trabecular failure strength and stiffness, these parameters will also be computed for the cortical compartment and whole bone (comprising trabecular and cortical bone) at the peripheral location (distal tibia) and the effects compared. Since μFE simulations also yield strain energy maps, from histograms of this parameter, means, median and mode will be computed as any of these could be more sensitive indicators of treatment than whole-section stiffness. Densitometric variables will be evaluated as well for the locations examined (proximal femur and L-spine by DXA), and distal tibia, and 38% tibial shaft (pQCT). Appropriate adjustments will be made for multiple comparisons to account for loss of power. Lastly, associations between baseline parameters as well as between the temporal changes in these parameters will be examined by linear regression.

Schedule of visits and evaluations

Visit Description						
Study Visits: Days or Weeks	Screening Visit	Additional Screening <i>*meets criteria</i> -2.5≤T≤+1	Baseline Visit	6 Month Visit	12 Month Visit	Study Completion
Informed Consent	X					
Demographics	X					
Medical History	X					
Prior Medications	X					
Height	X					
Weight	X					
Urine Pregnancy Test	X					

DXA Hip and Spine	X				X	
pQCT		X			X	
Blood Draw		X				
MRI Tibia and Spine			X		X	
Randomization			X			
Subject Instructed to Begin Use of Device			X			
Data Collection from Device				X	X	
Start Vitamin D3 and Calcium Carbonate			X			
Review Medical Status, supplement compliance and Daily Routine				X	X	
Adverse Events		X	X	X	X	X
Study Completion						X

Training plan

All study personnel have completed the CITI training program and certificates are filed in the regulatory binders. A delegation of responsibilities log has been created and is also filed in the regulatory binder. Study team meetings will be held regularly at the University of Pennsylvania to assure all study personnel are adhering to the protocol. Sub groups will meet as needed.

Recruitment, screening, and eligibility criteria

We plan to recruit subjects through mass mailings to zip codes within a 30-mile radius of the University of Pennsylvania, advertisements in local media, and flyers; methods that have been successful in our prior clinical trials. Inclusion criteria will be age 45-65 years and post-menopause, as defined by a history of amenorrhea for a minimum of 24 months and a serum FSH concentration of >25 mIU/mL. Exclusion criteria will be current or prior use of medications known to affect bone (i.e. bisphosphonates, calcitonin, selective estrogen receptor modulators, denosumab, diphenylhydantoin, or glucocorticoids), bone mineral density T score of less than -2.5 and greater than +2, vitamin D level less than 12 ng/ml, BMI of greater than 32, current alcohol or drug abuse, cardiac, pulmonary, liver, or renal disease or diabetes. Patients meeting the entry criteria at the screening or follow-up visit will be randomly allocated 1:1 to an active LMMS or a placebo device.

The PI and study staff will review subject accrual rates and adherence to inclusion/exclusion criteria on a monthly basis throughout the recruitment phase. Enrolled subjects who become subsequently ineligible will be reported. The recruitment strategies will be adjusted as needed to achieve the target subject characteristics. The PI and Safety Officer will review the data bi-annually to ensure that participants meet the goals outlined in the grant proposal.

Informed consent and HIPAA

Informed consent is an ongoing process, which is initiated at the first contact with the potential subject and the study team. The Study coordinator will provide a prospective volunteer with a brief explanation of the study in person or over the phone. If interested, the potential subject will schedule an appointment during which the combined informed consent and HIPAA authorization form will be reviewed and signed after all questions have been answered.

Randomization and blinding/unblinding procedures

Subjects meeting the entry criteria at the screening visit will be randomly allocated 1:1 to an active LMMS or a placebo device. The subjects will then be assigned a treatment number. Subjects name and study number will be kept in a password-protected database separate from other study records. Random numbers will be generated by a random number generator by the device manager who will maintain a database with even

numbers being assigned to treatment and odd numbers to placebo. This database will not be shared with the PI or other members of the study team before completion of the study.

Study Intervention

Active and placebo devices, previously manufactured by Juvent, Inc, will be available from a completed trial on children with Crohn's disease. The FDA has designated the risk pertaining to the device as "non-significant". Subjects will be stimulated mechanically for 10 minutes daily at a frequency of 30 Hz and acceleration of 0.3 g (fixed and not alterable by the subject). In a previous clinical trial involving postmenopausal women, there were no malfunctions detected during the entire year of the study. Upon their return, recalibration of the devices used in that trial showed 98% accuracy relative to start date calibration. To mask the active/placebo status of the devices, all devices are equipped with a small speaker that emits a 500 Hz audible tone. Adherence will be monitored by an inboard adherence monitor that documents date, time and duration of each use, and the adherence data will be transmitted via serial connector to a computer dedicated to this task and supervised by study's project manager. Subjects will also complete a web-based survey two days per week. Adherence feedback will be provided to study participants in bi-weekly intervals. Subjects will also be monitored in person during the six month and twelve month study visits to review adherence, supplementation compliance and to record adverse events.

Participant Retention

Data adherence with the prescribed LMMS regimen will be collected by the study team during the six month visit and the twelve month visit via a serial connector. The study team will be able to monitor the date, time and duration of each use. The Study coordinator will contact the subjects bi-weekly to discuss adherence and to provide support. Data will be summarized as the percent of prescribed number of minutes completed (percent adherence) in the study subjects. The study coordinator will contact all study subjects that fail to maintain an 80% adherence rate in order to identify obstacles to adherence and to develop strategies to improve adherence. The coordinator will review these data with the PI and study team on a monthly basis and reports will be provided to the safety officer quarterly.

Concomitant Medications

Patients who currently taking or who have previously taken medications known to affect bone such as bisphosphonates, calcitonin, selective estrogen receptor modulators, denosumab, diphenylhydantoin, or glucocorticoids will be considered for exclusion excluded from the study. In addition patients currently taking illicit drugs or abusing prescription medications will also be excluded. All medications will be reviewed and recorded during the screening visit. Any changes will be recorded at subsequent visits. The same applies to any change of dosage information (dose, frequency, route of administration) or indication.

Safety Reporting

Reports of any unexpected (headache, dizziness, blurred vision, motion sickness, abdominal pain, nausea, low back pain) and serious (events leading to hospitalization or death) adverse events will be prepared by the PI and sent to the safety officer, IRB, CTTC and NIAMS within 36 hours. Reports summarizing other adverse events will be prepared by the Sstudy coordinator and CTTC informatics and sent to the PI and safety officer bi-annually, as follows:

- Subjects will be asked to contact staff with any symptoms or complaints potentially related to the use of the LMMS device.
- Subjects will keep a written record of these symptoms or complaints in the same diary in which they record instances in which they are unable to use the LMMS device (e.g. vacation, illness).
- Adverse event data that are compiled bi-annually will capture any reported symptoms or complaints potentially related to the use of the LMMS device.

An adverse event form has been developed and will be used by the study staff to record any adverse events that may be related to the LMMS intervention. The clinical coordinator will prepare a summary of adverse events according to subject ID and the study statistician will generate a report of adverse event rates within

each study arm. These data will be provided to the PI and safety officer on a bi-annual basis. However, the PI and safety officer will remain blinded to treatment assignment unless the safety officer determines it is necessary to access this information.

Data and Safety Monitoring Activities

The monitoring plan includes the case report forms (CRF) and source data verification of efficacy and safety parameters, the frequency of monitoring visits, regulatory document review, device accountability and compliance review. Monitoring will be conducted according to the University of Pennsylvania sponsor-investigator standard operating procedures.

A report schedule has been developed to meet the goals of the DSMP in accordance with NIAMS guidelines. The report forms are included below. The frequency of data review for this study differs according to the data type and is summarized in the following table.

Data Safety Monitoring Plan: Report Schedule			
Type of Report:	Prepared By:	Provided To:	Frequency:
Unexpected and Related Serious Adverse Events that Increase Risk	PI	Safety Officer, IRB, CTRC, NIAMS	Within 36 Hours
Adverse Events (combined)	Clinical Coordinator, CTRC Informatics Core	PI, Safety Officer	Every 6 months
		IRB, CTRC	Annually
Patient Recruitment, Targets	Clinical Coordinator, CTRC Informatics Core	PI	Monthly
		Safety Officer	Every 6 months
		IRB	Annually
Subject Adherence with Intervention	Clinical Coordinator	PI	Monthly
		Safety Officer	Every 6 months
Data Quality, Deviation from Protocol	Clinical Coordinator, CTRC Informatics Core	PI	Monthly
		Safety Officer	Every 6 months
		IRB	Annually and as needed
Final Analysis: Safety and Efficacy	Statistician	PI, Safety Officer	100% accrual and follow-up

Study Compliance

The Juvent platforms will collect the study data electronically. The study team will be able to monitor the date, time and duration of each use. The study coordinator will contact the subject bi-weekly to discuss adherence and to provide support. Adherence data will be collected by the study team via a serial connector and will be supervised by the study coordinator. Adherence feedback will be provided to study participants in bi-weekly

intervals. Subjects will also be monitored in-person during the six month study visit and twelve month study visit to review adherence, supplementation compliance and to record adverse events.

Data Flow

Data will be collected and recorded during each study visit. This will be captured on source documents created for this study. All data collected during the course of the study will be entered into the REDcap database. Data and form checks/data processing will be conducted to assure completion, consistency and accuracy. The data will then be analyzed. Additionally, compliance data downloaded electronically from the Juvent devices will be collected and monitored for agreement with study participant self-reporting.

Retention of Study Documentation

Study records will be retained in accordance with institutional policies. Currently, the University of Pennsylvania requires all study records to be retained for a minimum of seven years after a trial ends.

Data Management

The computer system that will be utilized for this study will be REDcap. The following functions will be supported: Data tracking, data entry, data editing, updating, reporting and statistical analysis.

REDCap, a data capture and archiving system, provides protocol-focused data management solutions. Developed by Vanderbilt University and implemented by an academic consortium consisting of hundreds of academic research institutions, REDCap application's intuitive design and tailored clinical research workflows enable a research team to capture and manage data entirely within the research team (i.e., no need for a dedicated IT-based data manager). REDCap serves as a more secure and robust alternative to traditional Excel and Access databases.

Quality Control Procedures

Case report forms will be reviewed by the study coordinator on an ongoing basis for completeness, accuracy and documentation. Quality control procedures will include graphical displays of the data to identify outliers and case-by-case reviews of data that fall outside of the expected ranges for each variable. Magnetic resonance, DXA and pQCT scans will be analyzed and reviewed for quality within three weeks of the study visit. An image quality monitoring system has been put in place as a means to evaluate the adequacy of the acquired images for analysis. Status of data entry and review will be summarized bi-annually. A summary of this information will be provided in the bi-annual safety reports. Any protocol deviations will be reported to the IRB and a list of protocol deviations will be maintained and included with the bi-annual safety reports and annual IRB reports.

Study Completion and Close-out Procedures

Once the study has been closed to enrollment and all follow-up data have been collected, the study will be considered to be in the closeout phase. During this phase, the data will be prepared for final analysis, regulatory and reviewing bodies will be notified, the investigational product inventory will be reconciled, and final reports will be completed.

Closeout activities include, but are not limited to, the following:

- Verification that all study procedures have been completed, data have been entered, and the investigational product has been returned to the responsible party.
- Verification that all data queries have been resolved.
- Assurance that correspondence and study files are accessible for external audits.
- Verification that the Penn IRB has been notified of the study's completion; a copy of the notification and any subsequent correspondence will be filed in the study administrative file.
- Final reports will be completed.

Participant Notification

Study participants will be notified that their participation in the study is over at the last visit. The PI or study team member will thank the subject for their participation in the trial. If the participants wish to be informed as

to the study's results, a copy of the publication will be mailed or emailed to them, per the participants' request.

Policies

Confidentiality Procedures

It is the responsibility of the PI to outline and enforce participant confidentiality and data security guidelines. Study staff should be instructed in their responsibilities regarding data safeguards and cautioned against the release of data to any unauthorized individuals without checking with the NIAMS.

Participant confidentiality safeguards include:

- Electronic files: Data identifying participants that are stored electronically should be maintained in an encrypted form or in a separate file.
- Forms: Forms or pages containing personal identifying information should be separated from other pages of the data forms.
- Data listings: Protected health information (such as name, medical record number, etc.) will not be included in any published data listing.
- Data disposal: Computer listings that contain participant-identifying information will be disposed of in an appropriate manner.
- Access: Participant records will not be accessible to persons outside the site.
- Storage: Study forms and related documents retained both during and after study completion will be stored in a secure location.

Additionally, the following elements are required for computer security:

- Passwords: Passwords provide limitations on general access to computer systems and to the functions that individuals can use.
- User Training: Study staff with access to clinical computer systems will be trained in their use and in related security measures.
- System Testing: Prior to the use of a new computer system, and subsequent to any modifications, the system should be tested to verify that it performs as expected.
- System Backups: Backup copies of electronic data should be made at specified intervals. Backups should be stored in file cabinets or secure areas with limited access.

Publication Policy

The principal investigator will have primary authorship responsibility. The PI must check with NIAMS if there are plans to publish data before the study is over.

UNIVERSITY OF PENNSYLVANIA

RESEARCH SUBJECT INFORMED CONSENT AND HIPAA AUTHORIZATION FORM

Protocol Title: Osteoporosis Treatment Response Assessed by
Micromechanical Modeling of MRI

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You are being invited to participate in a research study. Your participation is voluntary which means you can choose whether or not you want to participate. If you choose not to participate, there will be no loss of benefits to which you are otherwise entitled. Before you can make your decision, you will need to know what the study is about, the possible risks and benefits of being in this study, and what you will have to do in this study. The research team is going to talk to you about the research study, and they will give you this consent form to read. You may also decide to discuss it with your family, friends, or family doctor. You may find some of the medical language difficult to understand. Please ask the research team about this form. If you decide to participate, you will be asked to sign this form.

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Osteoporosis Treatment Response Assessed by Micromechanical Modeling of MRI

Why am I being asked to volunteer?

You are being invited to participate in this research study because you are a healthy, female volunteer between the ages of 45-65 years who has not had a period for a minimum of two years.

What is the purpose of this research study?

The purpose of this research study is to gather information about the effects of low-magnitude mechanical stimulation (LMMS) on bone using new magnetic resonance imaging (MRI) techniques. LMMS will be provided in the form of a Juvent Dynamic Motion Therapy Platform, which looks similar to a large bathroom scale. You will stand on the platform for 10 minutes each day. One half of participating subjects will be randomized (like the toss of a coin) to a platform that provides actual vibrations; the other half will use a platform that does not provide actual vibrations. The actual vibrations cannot be felt. Neither you nor the study staff will know which device you will receive.

How long will I be in the study? How many other people will be in the study?

One hundred women will participate for a period of one year.

What am I being asked to do?

You will make four visits. The first visit is a screening visit. If you qualify for the study you will return for a baseline visit, a six month visit and a twelve month visit. You will be asked to stand on the Juvent Platform for a period of 10 minutes each day.

Screening Visit: You will come to The Children's Hospital of Philadelphia at 3400 Civic Center Boulevard. Here you will meet with the study coordinator to review and sign the consent form after all questions and concerns have been addressed. You will provide information about your health and medications, and your weight and height will be measured. You will have a urine pregnancy test to document that you are not pregnant. You will have a DXA exam. The DXA, or dual-energy X-ray absorptiometry, is a bone density test that measures the amount of mineral in your bone. You will lie on a table while the scanner passes over your head. If the results of this exam indicate that you do not have osteoporosis in your hip and spine, you will have a pQCT of the lower leg. The pQCT is another test for evaluating bone density. Your foot will be placed in the scanning machine. Both DXA and pQCT are non-invasive tests and take about 20-30 minutes to complete. You also will have blood drawn to test for blood chemistries, thyroid hormone, Vitamin D, a test for diabetes called hemoglobin A1c and FSH, a hormone that becomes elevated during menopause. The purpose of these blood tests is to find out if you have certain conditions that could cause bone disease and to confirm that you are postmenopausal. A total of five teaspoons of blood will be collected.

This screening visit should take one and one half to two hours.

Baseline Visit: If the blood tests show that you are eligible for the study, you will return for an MRI at the Hospital of the University of Pennsylvania. The MRI involves scans of two parts of your body; your spine and lower leg. These scans take approximately one hour. You will complete the MRI screening questionnaire to make sure that it is safe for you to have an MRI. You cannot have an MRI test if you have a cardiac pacemaker or certain types of metal implants or material in your body.

You will go to the MRI suite where you will change into a gown. You will lie on your back on a couch that will be moved into the center of the MRI scanner, which is open on both ends. Your whole body, except for your head, will be in the scanner. A scan of your lower leg will be performed. The scan involves placing your lower

leg in a plastic device that surrounds the lower leg, called a coil. The scan of your spine requires that you lie on your back and go into the scanner head first.

It is possible that you could be asked to return for a repeat MRI scan if there are technical difficulties with the initial scan.

During this visit you will meet with the device manager. The device manager will provide you with a Juvent Platform and you will be instructed in its use.

Remember that one half of participating subjects will be randomized (like the toss of a coin) to a platform that provides actual vibrations; the other half will use a platform that does not provide actual vibrations. The device manager will conduct the randomization. You will first be assigned a treatment number. Your name and study number will be kept in a password-protected database separate from other study records. Random numbers will be generated by a random number generator. The device manager will maintain a database with even numbers being assigned to the vibrating platforms and odd numbers to platforms that do not vibrate. This database will not be shared with the PI or other members of the study team before completion of the study.

You will be required to stand on the platform for a total of 10 minutes each day.

You should be aware that the study team will be able to monitor the date, time and duration of each use.

Calcium Carbonate and Vitamin D3 Supplementation

During the course of the study you will be asked to take 1200 mg/day of Calcium Carbonate and 1000 IU/day of Vitamin D3. These supplements are combined, therefore you will be taking a total of two pills a day. The pills are soft gel.

If you are unable to take the supplements provided due to difficulty swallowing, the study team will work with you to provide a different size/quantity of the supplements but with the same dosage.

At this baseline visit the study team will provide you with a supply of calcium carbonate and vitamin D3.

The study team will also provide you with a journal, we ask that you document any time you miss taking these supplements.

This visit will take about two and 1/2 hours.

Study Monitoring: The study coordinator will contact you either by phone or email (your preferred choice) every other week to discuss your daily sessions and any problems you may be having.

Six-Month Visit: You will return to the study site to review your medical status and daily routine. We ask that you bring your supplement bottles with you during this visit.

During this visit the study coordinator will count and record the amount of pills remaining, if any. Remaining supplements will be discarded and you will be given a new supply of supplements.

This visit will take one hour.

Twelve-Month Visit: You will return to the study site. We will repeat the DXA, pQCT and MRI studies and we will update your medical status and daily routine.

We ask that you bring your supplement bottles with you during this visit.

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During this visit the study coordinator will count and record the amount of pills remaining, if any. Remaining supplements will be discarded.

This visit will take about three hours.

If you have previous reports/results for DXA, pQCT, blood work, or MRIs, which meet our protocol requirements and were conducted within the 60 day window, then these results may be used/collected for the study. With your permission, the study team will review these results and decide if they meet study requirements.

Survey: So we can actively monitor your study compliance we are asking you to complete a weekly survey which will be sent to your email. In the event you do not have an email or prefer not to use email we will review the questions with you by phone.

What are the possible risks or discomforts?

Taking part in a research study involves risks or “side effects.” You should talk about these risks with the study staff. There may be side effects we do not know about yet.

MRI: The known risks associated with MRI are minimal. MRI uses radio waves and a magnetic field to take pictures. The magnet is always on. Some individuals may feel claustrophobic (uncomfortable in small spaces) during the MRI scan or may be disturbed by the sounds of the machine, which are loud and repetitive. We shall provide you with protective earplugs and make every attempt to ensure your comfort with blankets, etc. during your time in the scanner. Any metal objects on or inside your body may heat up, move and/or not function properly within the scanning room.

Implanted medical devices and metallic foreign fragments inside your body may pose a risk if you were to enter the MRI magnet room.

Devices such as pacemakers, internal cardiac defibrillators, insulin pumps, and other medical devices may also prevent you from safely having the MRI. Therefore, questions regarding medical and work history will be asked prior to your exam.

Another risk is that from a metallic object flying through the air toward the magnet and hitting you. There are many safety measures in place to reduce this risk, including screening of all persons and materials entering the scanning room. In addition, as the study begins, the door to the room will be closed to minimize the risk of someone accidentally walking into or bringing an object into the magnet room.

Some of the pulse sequences and/or RF coils are not FDA approved but are considered to pose no more than minimal risk. It is possible that during the course of the research study, the research staff may notice an unexpected finding. Should this occur, the finding will be considered by the appropriate personnel and the PI will inform you if necessary. These possible findings may or may not be significant and may lead to anxiety about your condition and to further work-up by your physician.

Exposure to Ionizing Radiation from DXA and pQCT: This research study involves exposure to radiation from the DXA and pQCT scans and therefore you will receive a small radiation dose. This radiation dose is not necessary for your medical care and will occur only as a result of your participation in the study. At doses much higher than you will receive, radiation is known to increase the risk of developing cancer after many years. At the doses you will receive, it is very likely that you will see no effects at all.

Reproductive Risks: Since the DXA and pQCT involve radiation, a negative urine pregnancy test will be required before a woman of childbearing potential can participate in this study. Although there are no known risks of MRI to a pregnant woman or a fetus, there is a possibility of yet undiscovered pregnancy related risks.

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Blood Draw: The blood sampling process infrequently causes pain, bruising, bleeding, vein infection and/or vein clotting at the site, and possible fainting. There is little risk of providing 5 teaspoons of blood in a healthy individual.

Juvent Platform: The Food and Drug Administration has designated the risk of this device as "non-significant".

Privacy and/or Confidentiality: Every effort will be made to protect your privacy and confidentiality. However, this can not be guaranteed.

We will provide you with copies of the DXA report and the lab test results to review with your doctor if you choose. It is possible that during the course of the research study, the research staff may notice an unexpected finding(s). Should this occur, the finding(s) will be considered by the appropriate study personnel. We will also provide you with a handout created by the study team and completed by the study team that outlines your results (both normal and/or abnormal results). We encourage you to discuss any findings with your physician.

What if new information becomes available about the study?

During the course of this study, we may find more information that could be important to you. This includes information that, once learned, might cause you to change your mind about being in the study. We will notify you as soon as possible if such information becomes available.

What are the possible benefits of the study?

There are no direct medical benefits to you if you take part in this study.

What other choices do I have if I do not participate?

You have the choice of not participating in the study. Your current and future medical care at the University of Pennsylvania will not be affected if you decide to not take part in this study.

Will I be paid for being in this study?

Yes, Payments will be made by check. You will be paid \$xx for the screening visit. If you qualify for the study, you will be paid a total of \$xx; \$xx for the Baseline visit, \$xx for the six month visit and \$xx for the 12 month visit. This payment is to reimburse you for expenses related to participating in the study, such as transportation and parking, and to compensate you for the time and inconvenience related to your participation. Please note: In order to be compensated for your participation in this study, you must provide your social security number. Additionally, please note that the University of Pennsylvania is required to report to the IRS any cumulative payments for participation in research studies that exceed a total of \$600 in a calendar year.

As previously mentioned the data collected on the Juvent Platforms will allow the study team to monitor the date, time and duration of each use. A bonus gift valued at \$xx (either check or gift card) will be given to all subjects that are 100% compliant (stand on device every day for the full 10 minutes).

Will I have to pay for anything?

All study-required procedures will be performed at no cost to you.

What happens if I am injured or hurt during the study?

We will offer you the care needed to treat injuries directly resulting from taking part in this research. We may bill your insurance company or other third parties, if appropriate, for the costs of the care you get for the injury, but you may also be responsible for some of them. There are no plans for the University of Pennsylvania to pay you or give you other compensation for the injury. You do not give up your legal rights by signing this form. If you think you have been injured as a result of taking part in this research study, tell the person in charge of the research study as soon as possible. The researcher's name and phone number are listed on the first page of this consent form.

When is the Study over? Can I leave the Study before it ends?

This study is expected to end after all participants have completed all visits, and all information has been collected.

The study doctor may take you out of the study at any time and for any reason. Some of the reasons the doctor may take you out of the study include:

- New information suggests that taking part in the study may not be in your best interest.
- You decide to take back your permission for us to collect, use or share your health information.
- You have not followed study instructions.

If you decide to participate, you are free to leave the study at any time. Withdrawal will not interfere with your future care.

Who can see or use my information? How will my personal information be protected?

We will do our best to make sure that the personal information obtained during the course of this research study will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

A description of this clinical trial will be available on <<http://www.clinicaltrials.gov>> as required by U.S. law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

Electronic Medical Records and Research Results

What is an Electronic Medical Record?

An Electronic Medical Record (EMR) is an electronic version of the record of your care within a health system. An EMR is simply a computerized version of a paper medical record.

If you are receiving care or have received care within the University of Pennsylvania Health System (UPHS) (outpatient or inpatient) and are participating in a University of Pennsylvania research study, results of research-related procedures (i.e. laboratory tests, imaging studies and clinical procedures) may be placed in your existing EMR maintained by UPHS.

If you have never received care within UPHS and are participating in a University of Pennsylvania research study that uses UPHS services, an EMR will be created for you for the purpose of maintaining any results of procedures performed as part of this research study. The creation of this EMR is required for your participation in this study. In order to create your EMR, the study team will need to obtain basic information

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about you that would be similar to the information you would provide the first time you visit a hospital or medical facility (i.e. your name, the name of your primary doctor, the type of insurance you have). Results of research procedures performed as part of your participation in the study (i.e. laboratory tests, imaging studies and clinical procedures) may be placed in this EMR. Once placed in your EMR, these results are accessible to appropriate UPHS workforce members that are not part of the research team. Information within your EMR may also be shared with others who are determined by UPHS to be appropriate to have access to your EMR (e.g. health insurance company, disability provider, etc).

The MRI performed under this protocol is not for medical purposes, and the images are not planned to be interpreted by a physician.

Please note that since some study procedures will also be conducted at the Childrens Hospital of Philadelphia the CHOP EMR may also capture this information.

What personal health information is collected and used in this study, and might also be disclosed?

The following personal health information will be collected, used for research and may be disclosed or released during your involvement with this research study: Name, address, birthdate, telephone number, email, medical record number, medical history, current and past medications or therapies, DXA, pQCT, and MRI images, and blood test results. Your social security number is required for payment only and is stored in a separate file.

Research records will be stored in secure areas. DXA, pQCT and MRI results will be filed using a subject ID rather than subject's name.

Why is your personal health information being used?

Your personal contact information is important for the University of Pennsylvania Health System and School of Medicine research team to contact you during the study. Your health information and results of tests and procedures are being collected as part of this research study.

Which of our personnel may use or disclose your personal health information?

The following individuals and organizations may use or disclose your personal health information for this research project:

- The principal investigator and the study team (other university staff associated with the study).
- University of Pennsylvania Office of Regulatory Affairs, (the committee charged with overseeing research on human subjects).
- The University of Pennsylvania Office of Human Research (the office which monitors research studies).
- Authorized members of the University of Pennsylvania, the University of Pennsylvania Health System and the University of Pennsylvania School of Medicine, as well as the Children's Hospital of Philadelphia workforce, who may need to access your information in the performance of their duties (for example: to provide treatment, to ensure integrity of the research, scheduling, accounting or billing matters, etc.).

Who, outside of the University of Pennsylvania Health System and the School of Medicine, might receive your personal health information?

Authorized members of The Children's Hospital workforce who may need to access your information in the performance of their duties.

As part of the study, the principal investigator may disclose information, including the results of the research study tests and procedures to sources outside the Health System, such as for an application for funding, journal publications, or scientific posters.

Results of the study will also be reported to authorized representatives from the NIH (National Institutes of Health).

It is possible that authorized members from the Office of Human Research Protection or other governmental agencies may want to review the records from this research study.

In all disclosures outside of the University of Pennsylvania Health System and School of Medicine, you will not be identified by name or any other direct personal identifier unless disclosure is required by law.

The principal Investigator or study staff will inform you if there are any changes to the list above during your active participation in the trial. Once information is disclosed to others outside the University of Pennsylvania Health System or School of Medicine the information may no longer be covered by the federal privacy protection regulations.

How long will the University of Pennsylvania Health System and the School of Medicine be able to use or disclose your personal health information?

Your authorization for use of your personal health information for this specific study does not expire. This information may be maintained in a research repository (database). The information collected as part of this study may be useful for other studies related to bone disease. We can only use this information again if the institutional review board, a committee set up by the University of Pennsylvania to protect the safety and privacy of research subjects allows us to do this. The committee may want us to talk to you again before we do another study using this information. However, the committee may allow us to use the information again without contacting you if we do not use any information that can identify you.

Will you be able to access your records?

You will be provided with the results of the DXA scan and any blood tests performed.

Can you change your mind?

You may withdraw your permission for the use and disclosure of any of your personal information for research, but you must do so in writing to the principal investigator at the address on the first page. Even if you withdraw your permission, the principal investigator for the research study may still use your personal information that was collected prior to your written request if that information is necessary to the study. If you withdraw your permission to use your personal health information that means you will also be withdrawn from the research study.

Who can I call with questions, complaints or if I'm concerned about my rights as a research subject?

If you have questions, concerns or complaints regarding your participation in this research study or if you have any questions about your rights as a research subject, you should speak with the principal investigator listed on page one of this form. If a member of the research team cannot be reached or you want to talk to someone other than those working on the study, you may contact the Office of Regulatory Affairs with any question, concerns or complaints at the University of Pennsylvania by calling (xxx) xxx-xxxx.

When you sign this form, you agree to take part in this research study. This means that you have read the consent form, your questions have been answered, and you have decided to volunteer. Your signature also means that you are permitting the University of Pennsylvania to use your personal health information collected about you for research purposes within our institution. You are also allowing the University of Pennsylvania to disclose that personal health information to outside organizations or people involved with the operations of this study.

A copy of this consent and HIPPA authorization form will be given to you.

Name of Subject (Print)

Signature of Subject

Date

Name of Person Obtaining
Consent (Print)

Signature

Date