Provide a short title for this study (200 characters or less):

ZEST (Zoledronic Acid in Frail Elders to STrength Bone)

<table>
<thead>
<tr>
<th>T1.0</th>
<th>Select the type of application:</th>
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<table>
<thead>
<tr>
<th>T2.0</th>
<th>Is the proposed research study limited to the inclusion of deceased individuals?</th>
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<tr>
<th>T2.1</th>
<th>Are any research activities being conducted at the VA Pittsburgh Healthcare System or with VA funds?</th>
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<td>Greater Than Minimal Risk</td>
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</table>
CS1.0 What is the reason for this submission?

New Research Protocol Submission

CS1.1 Has this research study been approved previously by the University of Pittsburgh IRB?

* yes

If the study expired or if this is a paper conversion, you are required to upload the last approved protocol and consent document, a completed Research Study Renewal Report Form found on the IRB website and a Data and Safety Monitoring Report.

Upload the last approved protocol, consent document, Renewal Report Form and Data and Safety Monitoring Report:

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<tr>
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</table>

Previous IRB #: 0612018

CS1.1.1 Has this research study (or a substantially similar research study) been previously disapproved by the University of Pittsburgh IRB or, to your knowledge, by any other IRB?

* no

CS2.0 Title of Research Study:

Maintenance of Skeletal Integrity in Frail Elders (Zoledronic acid in frail Elders to STrengthen Bone)

CS2.0.1 Requested approval letter wording:

CS2.1 Research Protocol Abstract:

This trial will examine the safety, efficacy and feasibility of a single dose of intravenous zoledronic acid in the maintenance of skeletal integrity for frail, institutionalized women, who are most at risk for the deleterious outcomes of osteoporosis. This is a 2-year, randomized, double-blind, calcium/vitamin D-controlled clinical trial of a single dose of therapy with at least 12 months follow-up. We will test the hypothesis that in institutionalized elderly women a
single dose of intravenous zoledronic acid therapy will: (1) be efficacious as demonstrated by
stability or improvement in bone mass measurements and reductions in bone turnover; (2) be
safe and feasible; and (3) provide estimates for vertebral and nonvertebral fracture reduction
in this cohort for use in planning a future study. All participants will receive calcium and
vitamin D throughout the trial. At baseline, up to 190 women will be randomized in a 1:1
allocation to zoledronic acid (group 1) or zoledronic acid placebo (group 2). At the end of 24
months, women will be followed to gather data on longer term fragility fracture rates and
survival until all participants have completed 24 months of follow-up.
Primary outcomes are (1) BMD of the total hip and spine; (2) markers of bone turnover; (3)
safety (adverse events and laboratory data) and feasibility; (4) participation and survival; and
(5) fragility fractures through 12 months. Secondary outcomes are BMD at other skeletal sites,
functional and cognitive assessments, comorbidity index and fragility fractures and survival
after 12 months.

[reviewer notes=]
CS3.8 Does this study include any personnel from Carnegie Mellon University, and/or use any CMU resources or facilities (e.g., Scientific Imaging and Brain Research Center (SIBR))?
* no

CS3.9 Is this your first submission, as PI, to the Pitt IRB?
* no

[reviewer notes-1]

CS4.0 List of Co-Investigators:

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<thead>
<tr>
<th>Last</th>
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<th>Organization</th>
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<tr>
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<td>Vujevich</td>
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<td>Wagner</td>
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<tr>
<td>Wright</td>
<td>Rollin</td>
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</tbody>
</table>

[reviewer notes-1]

CS5.0 Name of Primary Research Coordinator:

Dorothy Adams

CS5.1 Address of Primary Research Coordinator:

3471 Fifth Avenue, Suite 1110
Pittsburgh, PA 15213-3221

CS5.2 Telephone Number of Primary Research Coordinator:

412-692-2480

CS6.0 Name of Secondary Research Coordinator:

Mary Anne Ferchak

CS6.1 Address of Secondary Research Coordinator:

3471 Fifth Avenue, Suite 1110
Pittsburgh, PA 15213-3221

CS6.2 Telephone Number of Secondary Research Coordinator:

412-692-2475
CS6.3  Key Personnel/Support Staff (Only list those individuals who require access to OSIRIS):
    Last  First  Organization
    There are no items to display

CS7.0  Will this research study use any Pediatric PittNet or Clinical and Translational Research Center (CTRC) resources?
    yes

CS7.1  Please select the sites you intend to use:
    CTRC - Montefiore Hospital Clinical and Translational Research Center

CS8.0  Select the entity responsible for scientific review.
    External Scientific Review Completed – The scientific merit of this research protocol has been confirmed by an external scientific review committee as a condition of funding.

CS9.0  Does this research study involve the administration of an investigational drug or an FDA-approved drug that will be used for research purposes?
    *yes

CS9.1  Do you plan to utilize the Investigational Drug Service (IDS) to dispense the drug?
    *yes

CS10.0 Is this research study being conducted under a University of Pittsburgh-based, sponsor-investigator IND or IDE application?
    * no

If YES, you are required to submit the IND or IDE application and all subsequent FDA correspondence through the Office for Investigator-Sponsored IND and IDE Support (O3IS). Refer to applicable University policies posted on the O3IS website (www.o3is.pitt.edu).

CS11.0 Use the 'Add' button to upload one or more of the following:
    • the sponsor protocol (including investigator initiated studies) and/or
other brochures
  • the multi-center protocol and consent form template, if applicable

Name

Zoledronic Acid In frail Elders to Strengthen Bone (ZEST) 9/24/2008 3:33 PM

Is this research study supported in whole or in part by industry? This includes the provision of products (drugs or devices).

* no

Is this a multi-centered study?

* no

CSR0

Does your research protocol involve the evaluation or use of procedures that emit ionizing radiation?

* yes

HUSC GUIDANCE

REQUIREMENTS FOR THE REVIEW OF HUMAN SUBJECT RESEARCH PROTOCOLS BY THE
HUMAN USE SUBCOMMITTEE (HUSC), RADIATION SAFETY COMMITTEE

For Research Protocols Involving the Evaluation of Use of Diagnostic Procedures that Emit Ionizing Radiation:

Formal HUSC review/approval is required if the research protocol involves any of the following:

1. The use or evaluation of a radioactive agent or procedure that is not currently approved (i.e., for any clinical indication) by the FDA
2. The evaluation (i.e., for safety and/or effectiveness) of a FDA-approved radiopharmaceutical or procedure for an “off label” indication; or the use of a FDA-approved radiopharmaceutical or procedure for an “off label” indication if such use is experimental (i.e., not routinely performed in clinical practice).
3. Individuals (e.g., healthy volunteers) who would not be undergoing the procedure in association with the diagnosis or treatment of a disease or condition

Formal HUSC review/approval is not required if the diagnostic procedure is being performed, in a standard clinical manner and frequency, for screening or to evaluate the outcome of a treatment regimen. This would include diagnostic procedures for off-label uses that are routinely performed in clinical practice. 4,3

For Research Studies Involving the Use or Evaluation of Therapeutic Procedures that Emit Ionizing Radiation:

Formal HUSC review/approval is required if parameters (e.g., total radiation dose, dose fractionation scheme, etc.) of the radiation therapy procedure(s) are defined by the research protocol.

1 An “off-label” indication is a clinical indication which is not currently specified in the FDA-approved product labeling.
2 The risks of radiation exposure associated with the diagnostic procedure must continue to be addressed in the protocol and consent form using the HUSC-accepted wording.
3 The University of Pittsburgh IRB, at its discretion, may request formal HUSC review of the
research protocol.

**For any questions related to these requirements or their application, contact the Chair of the HUSC (412-383-1399) or the University’s Radiation Safety Office (412-624-2728)**

**CS12.1 After reviewing the HUSC guidance above, does your research protocol require HUSC review?** (Note: University of Pittsburgh’s Radiation Safety Committee oversight is limited to UPMC Presbyterian-Shadyside, Magee Women’s Hospital of UPMC, Children’s Hospital of Pittsburgh-UPMC, and Hillman Cancer Center. If other sites, you will be required to obtain approval from your radiation safety officer. Please contact askirb@pitt.edu for more information.)

* yes

Upload Radiation Forms:

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</table>

**CS13.0 Does this research study involve the deliberate transfer of recombinant DNA (rDNA) or DNA or RNA derived from rDNA into human subjects?**

* no

Upload Appendix M of NIH Guidelines:

<table>
<thead>
<tr>
<th>Name</th>
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**CS14.0 Are you using UPMC facilities and/or UPMC patients during the conduct of your research study?**

* yes

If Yes, upload completed Research Fiscal Review Form:

<table>
<thead>
<tr>
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<td>Fiscal Review Form</td>
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</table>

**CS15.0 Indicate the sites where research activities will be performed and/or private information will be obtained.**

Choose all sites that apply and/or use Other to include sites not listed:

**Sites:**

<table>
<thead>
<tr>
<th>UPMC</th>
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**Other |
UPMC
Sites:
- UPMC Presbyterian
- UPMC Passavant
- Other UPMC Site- Specify below:

Participating Nursing Homes and Assisted Living Care Facilities

If you selected School, International or Other, list the sites:
Participating Nursing Homes and Assisted Living Care Facilities

*For non Pitt or UPMC entities, upload documents granting permission to conduct research at that site:

<table>
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</table>

CS15.1 Have you, Susan Greenspan, verified that all members of the research team have the appropriate expertise, credentials, and if applicable, hospital privileges to perform those research procedures that are their responsibility as outlined in the IRB protocol?

* yes

CS15.2 Describe the availability of resources and the adequacy of the facilities to conduct this study:

* ...

[reviewer notes-]

CS16.0 Special Research Subject Populations:

Categories
Decisionally impaired

[reviewer notes-]

CS17.0 Does your research involve the experimental use of any type of human stem cell?

* no
1.1 Objective: What is the overall purpose of this research study? (Limit response to 1-2 sentences.)
We postulate that in frail institutionalized women a single dose of intravenous zoledronic acid, an antiresorptive therapy for osteoporosis, will: (1) be efficacious as demonstrated by maintenance or improvements in conventional bone mass measurements and reductions in bone turnover; (2) be safe and feasible; and (3) provide estimates for fracture reduction in this cohort for use in planning a future study. This trial will examine the safety, efficacy and feasibility of a single dose of intravenous zoledronic acid in the maintenance of skeletal integrity for frail, institutionalized women, who are most at risk for the deleterious outcomes of osteoporosis. This will allow us to determine the biologic efficacy at 12 months, while providing longer term safety and efficacy data after a single dose of medication. This study will provide the evidence needed to justify a future multi-center fracture reduction trial and to appropriately design such a study in this cohort if we demonstrate positive findings. Future studies could be designed to determine if a single dose upon entry into a nursing home is efficacious for this frail group.

Participants will be given the option to continue in a 1-year extension phase which will allow for the collection of additional bone health data at Month 36.

In a subset of 60 subjects (30 subjects receiving zoledronic acid and 30 on placebo enrolled in the parent study), we will assess trabecular bone microarchitecture using MRI technology (81-83). We hypothesize that in frail, elderly nursing home residents with osteoporosis (1) antiresorptive therapy will preserve trabecular microarchitecture in addition to bone mass assessed by standard DXA; (2) intact trabecular microarchitecture will be associated with greater bone mineral density (BMD) and low bone turnover both at baseline and in terms of change over time; and (3) intact trabecular microarchitecture will be associated with fewer fractures.

1.2 Specific Aims: List the goals of the proposed study (e.g., describe the relevant hypotheses or the specific problems or issues that will be addressed by the study).

a. Primary Objectives:

Specific Aim 1: To evaluate the efficacy of zoledronic acid to stabilize or improve bone mass and reduce bone turnover in frail elders (hypothesis 1), bone mass at the spine and hip will be measured at baseline, 6 and 12 months by dual-energy X-ray absorptiometry (DXA). We will evaluate biochemical markers of bone resorption and formation at baseline, 6 and 12 months. We will also assess bone density and bone turnover markers at 24 months during the follow-up to determine whether differences in BMD are maintained over 24 months. We will assess bone density and bone turnover markers at 36 months for participants in the 1-year extension phase.

Specific Aim 2: To address hypothesis 2, we will examine adverse events and laboratory safety values at regular intervals for up to 24 months after therapy. For participants in the 1-year extension phase, we will also examine adverse events and laboratory safety values for up to 36 months after therapy. For feasibility we will determine the participation enrollment rate, dropout rate, compliance and participation in follow-up visits to assess outcomes and survival rates for up to 24 months after randomization.

b. Secondary Objectives:

Specific Aim 3: We will collect data on vertebral fracture rates assessed by standard radiologic techniques in years 1 and 2, and in year 3 for participants in the 1-year extension phase. Reports and radiologic evidence of all other nonvertebral clinical fragility fractures, and medical history information on bone health and mortality will be collected until all participants have completed 24 months of follow-up to obtain estimates on fracture rates for a more
Section: Section 1 - Objective, Aims, Background and Significance

definitive future reduction study.

c. High Resolution Wrist MRI Substudy Objectives:

We will examine bone microarchitecture using microMRI technology in a subset of 60 participants in the parent study (30 on zoledronic acid and 30 on placebo). Our specific aims will be to examine the association of microMRI derived topological parameters of microarchitecture at a radial site at baseline and 12 months. Our primary specific aim (1) is to examine the association of bone biopsy derived topological parameters at a radial site rich in trabecular bone with standard DXA-derived BMD measurements at the hip, forearm, and spine. We will compare changes in BMD in patients on and off therapy with zoledronic acid and compare those to MRI-derived indices over 1 year; (2) We will examine the association of microarchitecture characteristics with bone turnover at baseline and 12 months in patients on zoledronic acid or placebo; and (3) we will examine the trend for development of vertebral and nonvertebral fractures with changes in microarchitecture parameters at baseline and 12 months.

1.3 Background: Briefly describe previous findings or observations that provide the background leading to this proposal.

Background Information and Significance:

Impact of Osteoporosis and Fractures in Nursing Home Residents: Although osteoporosis is a devastating condition for women of all ages, its effects are even more significant in the elderly. In the U.S., there are over 250,000 hip fractures annually (1, 2), and 1 in 3 individuals over the age of 90 will sustain a hip fracture (3). This event is associated with an up to 20% chance of death in the subsequent year (4). One-quarter of patients are ultimately institutionalized, and less than half of them fully recover (4). Because the fastest growing segment of the U.S. population are women over the age of 85 years, the number of patients with hip fractures is expected to double in the next 15 years (5, 6).

The impact of osteoporosis for residents in the nursing home is even more dramatic. Nearly 2 million persons (mean age 84) live in long term care facilities in the U.S.; for every resident in a long term care facility, there are 2-3 elderly individuals with similar functional impairment who are supported in the community (7). Based on bone density assessments, community-dwelling women (age >80 years old) have a prevalence of osteoporosis of 52% (8), women living in nursing homes have a prevalence of osteoporosis of 85% (9, 10, 11). While the rate of nonvertebral fractures in the community is 2-3% per year, it is approximately 11% per year in the nursing home (11). In follow-up, nursing home residents who fractured at any site were hospitalized more than 15 times as often as those who did not (12). The rates of emergency department use and contact with healthcare providers were also increased. Fracture represents a major, if not the final insult, to an already compromised and frail patient.

There are few data on vertebral fractures in nursing home residents. In the community, vertebral fractures account for 500,000 fractures annually (13). A vertebral fracture is associated with a greater incidence of future fractures (double-to-triple the risk) (14, 15), back pain (16-19), decreased mobility, increased days at bed rest, decreased time at work (20), and higher rates of hospitalization and mortality (21, 22). Vertebral fractures significantly impact on the quality of life and are associated with decreased activities of daily living, depression, lower self-esteem, and social impairment (23-27). Given the multiple pre-existing medical conditions in frail, institutionalized individuals, it is likely that a vertebral fracture would have a much greater impact, resulting in further loss of independence.

Despite the significant impact and consequences of fractures, there are relatively few data on osteoporosis treatment in nursing home residents. In fact, most investigations have been conducted outside of the U.S.; only four studies have included older, frail Americans (28-31). Two recent large clinical trials in community-dwelling elderly men and women over age 70 years (3,314 and 5,292 participants), also found no hip fracture reduction with supplementary
Section: Section 1 - Objective, Aims, Background and Significance

calcium and 800 IU vitamin D (32, 33). Therefore, even the benefit of supplementary calcium and vitamin D is controversial. These new studies have important clinical ramifications because calcium and vitamin D are now the standard of care.

Summary of Therapeutic Options for Osteoporosis Treatment In Frail Elders: The currently available therapies are less than ideal for use in frail, institutionalized women. Hormone replacement can increase cardiovascular, coagulation, and breast cancer risks (34). Selective Estrogen Receptor Modulators (SERMS) must be discontinued in women with immobility (35) and have not been shown to reduce nonvertebral fractures (36). The efficacy of calcitriol has been questioned (37, 38). Parathyroid hormone may improve bone density and reduce fractures (39), but the cost and staff time to administer this medication to frail nursing home patients is prohibitive (40). Weekly or monthly oral bisphosphonates are efficacious for elderly women, but would require nursing observation for 30-60 minutes following administration and may produce gastrointestinal adverse events in this cohort (41, 42).

Intravenous ibandronate would require an infusion every 3 months. Therefore, the most viable option would be a single infusion given over approximately 60 minutes of intravenous bisphosphonate such as zoledronic acid.

Zoledronic acid, a potent intravenous bisphosphonate, is FDA-approved for the treatment of hypercalcemia of malignancy and for the treatment of osteoporosis. Overall, since zoledronic acid has the potential to markedly increase bone mass and decrease bone turnover after one intravenous dose, it would be an optimal and feasible therapy for frail, elderly women in the nursing home.

There are limited data on BMD and fractures in frail residents in long term care, and there are no data on zoledronic acid in this very frail population. There are data demonstrating a single dose of zoledronic acid has a positive effect on skeletal health over three years in young postmenopausal women. The 1-year extension phase will be the first opportunity to examine if a single dose of zoledronic acid will maintain bone mass over three years in this frail cohort.

Determinants of Bone Strength: Although bone mineral density contributes significantly to bone strength, other factors such as bone turnover, connectivity and mineralization contribute to fracture risk (49, 50). In addition to bone mass and collection of fragility fractures, it will be important to examine alternative factors that contribute to fracture risk reduction, such as changes in bone turnover.

High Resolution Wrist MRI Substudy: The current gold standard technology to evaluate the efficacy of a therapeutic agent for osteoporosis is bone mineral density assessed by Dual Energy X-ray Absorptiometry (DXA). Bone mineral density, however, only explains about 60% of fracture risks (47, 84-86). Other factors such as trabecular microstructure contribute significantly to bone strength and determine fracture risk (47, 87). Until recently, bone microarchitecture could only be assessed by an invasive iliac crest bone biopsy. A novel technique, Virtual Bone Biopsy (VBB), has been developed which for the first time can assess trabecular bone microarchitecture using MRI technology (81-83). Several studies have demonstrated that the number of connected trabeculae or connectivity are more important than the thickness of the trabecular bone mass. Using finite element analysis of a 2-dimensional model of human vertebral trabecular bone, investigators examined trabecular strength. They compared the reduction in the number of trabeculae versus reduction in the thickness of trabeculae (88). If they randomly removed longitudinal trabeculae to achieve a reduction in bone density of 10%, there was a 70% reduction in bone strength. If they removed the same amount of bone by uniformly removing the thickness of the longitudinal trabeculae however, strength was reduced by only 20%. This demonstrated the importance of connectivity in the preservation of bone strength independent of bone density. Investigators have tried to examine this component of bone strength by trabecular bone biopsy. Kleerekoper compared microstructural indices from iliac trabecular bone biopsies in 26 patients with vertebral fractures compared to 24 controls (89). Postmenopausal women with vertebral fractures had significantly lower trabecular plate density, an index in the number and connectivity of structural elements. He concluded that the structural confidence of the trabeculae was dependent not only on the absolute amount of bone but on the trabecular
connectivity and microstructure. Other investigators have supported this with computational models (90). Therefore the microstructure of trabecular studies to examine trabecular bone contributes significantly to bone strength independent of bone mass. This data highlights the need for studies to examine trabecular microarchitecture of frail elderly women who have a high risk and prevalence of fractures. These types of studies will ultimately provide a greater understanding of the response to antiresorptive therapy in older women.

Virtual bone biopsy (VBB) by micromagnetic resonance imaging (microMRI) was developed at the University of Pennsylvania (81-83). This device provides three-dimensional images of bone microarchitecture in addition to bone mass. Virtual bone biopsy has emerged as a modality for performing in vivo histomorphometry, or a bone biopsy, non-invasively. Wehrl and colleagues examined 79 women ages 28-78 years (mean age 54 years) with VBB of the forearm (91). They also examined women for vertebral fractures. Although there were no differences in standard DXA of the spine, femoral neck, or trochanter between women with a vertebral fracture and those without, they reported significant differences in the radial virtual bone biopsy-derived indices between those with a vertebral fracture and those without. For example, those with vertebral deformities had a lower ratio of plate-like to rod-like trabeculae than those without vertebral deformities. The number of intact trabecular rods was also lower in the vertebral deformity group.

1.4

Significance: Why is it important that this research be conducted? What gaps in existing information or knowledge is this research intended to fill?

Use of Osteoporosis Medications in Pittsburgh Nursing Homes: In preparation for this proposed study, we contacted nursing homes in the greater Pittsburgh area (many will participate in this study), and obtained data regarding the use of osteoporosis therapies, including calcium and vitamin D and medications causing bone loss. Pharmacy data was not available on all residents. Approximately 10.7% of patients were treated with an effective osteoporosis medication. We excluded calcitonin nasal spray, a drug not supported by the NIH Consensus Conference on Osteoporosis, but prescribed in 3.6% of these patients. Assuming that 85% had osteoporosis, approximately three-quarters who qualified for effective therapy were untreated. Moreover, only 24.7% of patients were receiving supplementary calcium and 2.8% of patients were receiving supplementary vitamin D, the current standard of care. Furthermore, patients on glucocorticoids (2.9%) and anti-epileptic drugs (7.2%) would be at greater risk for osteoporosis. These data demonstrate that osteoporosis treatment is minimal in this population and support the need for a trial assessing the safety and efficacy of an annual intravenous agent in this cohort.
Section: Section 2 - Research Design and Methods

2.1 Does this research study involve the use or evaluation of a drug, biological, or nutritional (e.g., herbal or dietary) supplement?
   * Yes

2.1.1 Does this research study involve an evaluation of the safety and/or effectiveness of one or more marketed nutritional (e.g., herbal or dietary) supplements for the diagnosis, prevention, mitigation or treatment of a specific disease or condition or symptoms characteristic of a specific disease or condition?
   * No

2.1.2 Does this research study involve the use or evaluation of one or more drugs or biologicals not currently approved by the FDA for general marketing?
   * No

2.1.3 Does this research involve the use or an evaluation of the effectiveness and/or safety of one or more drugs or biologicals currently approved by the FDA for general marketing?
   * Yes

2.1.3.1 Are the FDA-approved drugs or biologicals being evaluated in this research study for a new clinical indication, different population, or route of administration and/or dosage level that is not currently specified in the FDA-approved product labeling?
   * Yes

If you respond Yes, an IND number or the FDA written concurrence of IND exemption may be required.

2.1.3.1.1 By using the "Add" button available below, list and specify the following for each of the FDA-approved drugs or biologicals being evaluated under this research study.
   - Whether data from this research will be reported to the FDA in support of a new indication for the use of this drug product or to support any other significant change in the labeling (i.e., new indication). If Yes, provide the corresponding IND number.
   - Whether data from this research will be used to support a significant change in the advertising for this drug product (i.e., new advertisement). If Yes, provide the corresponding IND number.
   - Whether the proposed 'off-label' evaluation of the approved drug is felt to significantly increase the risks (or decrease the acceptability of risk) compared to the current approved uses of this drug or biological. If Yes, provide the corresponding IND number. If No, provide a justification for why the risk is not increased or the acceptability of risk is not decreased (i.e., risk justification).
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<table>
<thead>
<tr>
<th>Approved Drug/Biologic</th>
<th>New Indication</th>
<th>New Advertisements</th>
<th>Risk Concern</th>
<th>Risk Justification/No IND</th>
<th>IND #</th>
</tr>
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<tbody>
<tr>
<td>Zoledronic Acid (Reclast)</td>
<td>no</td>
<td>no</td>
<td>The study drug is not being used off-label; it is approved for the treatment of osteoporosis, which is how it is being used in this study.</td>
<td>The FDA granted a waiver for an IND for this study since (1) the route of administration, dosage level, patient population, and other factors do not significantly increase the risks or decrease the acceptability of the risks, and (2) informed consent is secured, and (3) the study was not begun until it was reviewed and approved by an IRB, and (4) the investigation is conducted in compliance with the requirements of 21 CFR 312.7. We have uploaded the letter of 10/19/2007 granting the exemption from the requirements of Part 312 of the IND regulations and an IND is not required.</td>
<td></td>
</tr>
</tbody>
</table>

Upload information on FDA approved indications/doses and FDA exemption letter if applicable:

<table>
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<th>Name</th>
<th>Modified Date</th>
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<tbody>
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</tr>
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<td>Package insert for Reclast 2009</td>
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</tr>
<tr>
<td>FDA letter granting IND exemption</td>
<td>10/6/2008 2:10 PM</td>
</tr>
</tbody>
</table>

[reviewer notes -]

#### 2.2 Will this research use or evaluate the safety and/or effectiveness of one or more devices?

* no

[reviewer notes -]

#### 2.3 Summarize the general classification (e.g., descriptive, experimental) and methodological design (e.g., observational, cross-sectional, longitudinal, randomized, open-label single-blind, double-blind, placebo-controlled, active treatment controlled, parallel arm, cross-over arm) of the proposed research study, as applicable.

Study Design:

This is a 2-year, randomized, double-blind, calcium/vitamin D-controlled clinical trial of a
single dose of therapy with at least 12 months of follow-up in elderly women 65 and older who reside in nursing homes or assisted living facilities. All participants will receive calcium and vitamin D throughout the trial. At baseline, up to 190 women will be randomized in a 1:1 allocation to zoledronic acid (group 1) or zoledronic acid placebo (group 2). At the end of 24 months, women will be followed to gather data on longer term fragility fracture rates and survival until all participants have completed 24 months of follow up (Appendix 4: Research Design & Methods Table and Figure 4). Participants will be given the option to continue in a 1-year extension phase which will allow for the collection of additional bone health data at Month 36.

High Resolution Wrist MRI Substudy Design:
A subset of patients from the parent study will be enrolled in the substudy. We will recruit 60 women including 30 who have been randomized to placebo and 30 who have been randomized to zoledronic acid. Inclusion and exclusion criteria will be similar to the parent study. However, only cognitively intact women will be included in the substudy due to the need for cooperation in the MRI procedure. The study statistician will provide the research team with the allocation numbers for recruitment to ensure equal numbers of women on active treatment and placebo. After written informed consent has been obtained for the substudy, participants will have the micro MRI assessments performed at the University of Pittsburgh MRI Research Center. They will be transported by ambulance or chair car service and accompanied by an escort for the microMRI procedure, which will be performed at baseline and month 12.

2.3.1 Does this research study involve a placebo-controlled arm?

* yes

[reviewer notes: ]

2.3.1.1 Is there a commonly used diagnostic/treatment approach that is currently recognized as being effective for the proposed subjects' disease or condition, and that will be withheld from subjects assigned to the placebo arm of this research study?

No; there is no commonly used diagnostic/treatment approach that is currently recognized as being effective for the proposed subjects' disease or condition

[reviewer notes: ]

2.4 Will any research subjects be withdrawn from known effective therapy for the purpose of participating in this research study?

* no

[reviewer notes: ]

2.5 Will screening procedures (i.e., procedures to determine research subject eligibility) be performed specifically for the purpose of this research study?

* yes

2.5.1 List the screening procedures that will be performed for the purpose of this research study. Do NOT include the inclusion/exclusion criteria in this section as they will be addressed in section 3; questions 3.13 and 3.14.

Screening and Randomization:
After informed consent for screening has been obtained, the screening visit will be conducted at the participant's care facility. Procedures performed at the screening visit include history
and physical exam; dental exam; electrocardiogram; Food Frequency Questionnaire to assess dietary calcium intake; functional assessments [Activities of Daily Living (ADL), Binner Nursing Home Physical Performance Test (NHPPT) (77)] and cognitive assessments [Short Portable Mental Status Questionnaire (SPMSQ), comorbidity index]; Patient Health Questionnaire (PHQ-9); clinical fracture query; blood draw of approx. 20 ml for screening and safety labs (general health measures, kidney and liver function), and bone mineral metabolism (PTH, 25-hydroxyvitamin D); and heel ultrasound. A gait belt will be used for patient safety during the physical performance testing. This screening visit will take approx. 4 hours.

Screening is a staged process and may occur over several visits in order to accommodate patient schedules and needs. The DXA (spine, hip, wrist, total body, Vertebral Fracture Assessment (VFA) and 3D hip) is the final stage of screening testing and will be completed before proceeding with any of the randomization procedures.

[reviewer notes—]

2.6 Provide a detailed description of all research activities (e.g., all drugs or devices; psychosocial interventions or measures) that will be performed for the purpose of this research study.

This description of activities should be complete and of sufficient detail to permit an assessment of associated risks.

At a minimum the description should include:

- all research activities
- personnel (by role) performing the procedures
- location of procedures
- duration of procedures
- timeline of study procedures

Location and Duration:
All screening and study visits will be performed at participant's care facility (screening, randomization, Day 1, Day 2, Month 6, Month 12, and Month 24). DXA scans, which take approximately 1 hour, will be performed using a portable DXA unit. Depending on available space at the nursing homes and care facilities, DXA scans will be performed on the portable DXA machine either inside the facility or in the mobile DXA unit. Dental exams, which will take approx. 30 minutes, will be performed at the care facility by Dr. Famili, a dentist co-investigator on this study, or by residents from the periodontal department under her supervision, at Screening and Months 12 and 24. Participants will be given the option to continue in a 1-year extension phase involving a Month 36 visit. Participants in the high resolution wrist MRI substudy will have the microMRI assessments performed at the University of Pittsburgh MRI Research Center at baseline and month 12, where they will be transported by ambulance or chair car service and accompanied by an escort.

It is possible that the blood tests performed as part of the study visits may need to be repeated, as described in the informed consents and Addendum #2 (also see protocol section G.3: Recruitment Methods and Consent Procedures, regarding Addendum consents). These repeat blood tests would be performed as soon as possible after the need for retesting became apparent. The repeat blood draws would be performed at the participant’s care facility by the nurse coordinators or qualified research staff trained in phlebotomy. (See Appendix 1, Procedures & Locations Table, for detailed information)
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If assessments for function (ADL, NHPPIT), cognition (SPMSQ, Duke Co-morbidity Index Questionnaire) or depression (PHQ-9) are interrupted by patient needs before completion at follow-up visits for M12, M24, and M36 the test will be repeated from the beginning at the next opportunity for that study visit as these visits may occur over several days to accommodate patient needs and patient schedules (see Procedures and Location Table below). These are minimal risk assessments involving questionnaires and routine activities of daily living (see OSIRIS Section 2.8 for further description).

The randomization visit will be performed at the care facility and informed consent will be obtained prior to any study procedures being performed. Potential risks and benefits will be described orally and in writing. Those consenting to participate for the study will be required to sign an informed consent form describing the nature, purpose, design and risk/benefit ratio of this study, and the certification of informed consent statement will be signed by the PI or physician co-investigator.

Eligible subjects will be randomized in a 1:1 ratio to either 5 mg IV zoledronic acid or placebo given in a single dose, which will be administered via an inserted venous catheter. The study drug and placebo will be prepared by the UPMC Investigational Drug Service (IDS). This randomization visit will take approximately 3 hours where the following will be performed: blood draw (approx. 20 ml) for indices of bone mineral metabolism, bone markers, and safety labs; brief physical and vital signs (temperature, pulse, blood pressure); queries about health status changes, falls or fractures since screening visit; Calcium and vitamin D supplementation provided; and Tylenol will be administered 1 hour prior to the study drug infusion and to be given every 6 hours for the next 72 hours.

Following the infusion of zoledronic acid, the study coordinator or facility nurse will visit the patient daily for two days and ascertain any signs or symptoms that have appeared or worsened since the infusion (such as such as redness, bruising, warmth, bleeding or rash at the infusion site; flu-like symptoms; and any expected or unexpected adverse events potentially related to the intravenous zoledronic acid or placebo).

Outcome Variables and Measurements:
Primary Endpoints: Primary outcomes are 1) BMD of the total hip and spine, 2) markers of bone turnover, 3) safety (adverse events and laboratory data) and feasibility, 4) participation and survival, and 5) fragility fractures through 12 months.

Secondary Endpoints: Secondary outcomes are BMD at other skeletal sites, functional and cognitive assessments, comorbidity index and fragility fractures and survival after 12 months.

Skeletal Assessments:
Bone Mineral Density: We will assess bone mineral density of the hip (3D hip, total hip, femoral neck, trochanter, intertrochanter), spine (PA and lateral projections), forearm, Vertebral Fracture Assessment (VFA), and total body at baseline, 6, 12 and 24 months by mobile DXA unit using a Hologic Discovery A densitometer (Hologic, Inc., Bedford, MA). We will also assess heel ultrasound to determine if differences can be seen in patients on therapy as measured using a heel ultrasound device in a frail population and correlate with results of standard DXA (screening, Months 12 and 24). Participants in the 1-year extension phase will also have these BMD assessments by DXA and heel ultrasound at Month 36. We will also examine Hip Structural Analysis (HSA) by Beck and colleagues, which is a DXA derived analysis of hip geometry.

Indices of Bone Mineral Metabolism: Because bone mineral metabolism is altered with age, we will determine if the response in these indices to intravenous zoledronic acid is intervention-dependent. The monitoring of these parameters of bone mineral metabolism will further clarify our understanding of the pathophysiology of bone turnover in frail elderly women. Serum will be assayed for 25-hydroxyvitamin D2 and D3, and serum parathyroid hormone. To assess bone resorption, we will measure serum CTX and P1NP. Serum will be archived and possibly...
assayed at a later date for the marker of bone formation, bone-specific alkaline phosphatase (BSAP), osteocalcin, and possible future assessments of bone status. Serum for indices of bone mineral metabolism and markers of bone formation will be collected at months 0, 6, 12 and 24, and batch assayed. Participants in the 1-year extension phase will also serum collected for indices of bone mineral metabolism and markers of bone formation at month 36. Additional serum will be archived for future assessment of biochemical markers. Archived samples will be labeled with unique codes and will be stored for an indefinite period of time in a locked storage room at Montefiore Hospital in the freezers belonging to the PI. These freezers and the storage area are monitored by Vector Security alarm service. The information linking the assigned code numbers will be kept in a separate secure area at the Osteoporosis Prevention and Treatment Center. Only samples without identifiers will be shared with secondary investigators.

Vertebral Fractures: We will use the presence of vertebral fractures of the thoracic or lumbar spine as determined by Vertebral Fracture Assessment (VFA) performed by DXA (baseline, M6, M12, M24), which assesses vertebral fractures from T6 to L4, as the primary classification of vertebral fracture. Participants in the 1-year extension phase will also have VFA by DXA performed at month 36. The fractures will be scored according to the method of Genant (62, 63) and considered a grade 1, mild vertebral deformity (approximately 20-25% reduction in anterior, middle or posterior height), a grade 2, moderate vertebral deformity (25-40% reduction in any height) or a grade 3, severe vertebral deformity (>40% reduction in any height).

Fragility Fractures: From baseline to the end of follow up, all subjects will be queried every 6 months regarding clinical fragility or non-traumatic fractures. A fragility fracture is defined as a fracture following a fall from standing or sitting height. All reported fractures will be verified by obtaining the radiology report confirming the fractures. after the Month 24 study visit, women will be followed to gather data on longer term fragility fractures and survival until all participants have completed 24 months of long-term follow-up.

Skeletal microarchitecture Assessments: Micro magnetic resonance imaging (MicroMRI) is a new field of clinical microscopic imaging technology that is noninvasive and has the capacity to measure trabecular bone microstructure in vivo (i.e., a virtual bone biopsy) (81, 82, 91). The system uses a patented algorithm that transforms data into a highly detailed, three-dimensional model of bone microstructure similar to that of an invasive bone biopsy (Figure 1, Appendix 3) (82, 83). A coil was installed in the University of Pittsburgh research MRI equipment for these assessments. The microMRI will assess the right distal forearm using a Sigma 1.5 Tesla scanner (GE Medical Systems, Milwaukee, WI). The reproducibility and error sources of MicroMRI have previously been described (83). The technique permits quantification of the degree to which trabecular plates (surfaces) have deteriorated to become rods (curves), a change that characterizes osteoporosis. The parameter expressing this relationship is denoted surface-to-curve ratio. It is obtained after the image data have been subjected to a cascade of processing steps so that the plates are converted to surfaces and rods to curves. Using a unique algorithm, each image voxel can then be classified as belonging to a surface or curve or junction between the two fundamental topological types (Table 2, Appendix 3). Similarly, an erosion index is determined that represents the ratio of voxels expected to decrease during resorptive bone loss, divided by those that are expected to increase.

Safety:
Safety Labs: Safety labs will be assessed at screening, randomization, Day 2, Months 6, 12 and 24 visits and will include BUN, serum calcium, serum creatinine, liver function tests, alkaline phosphatase, albumin, TSH, 25 hydroxyvitamin D, hematocrit and hemoglobin, and estimated GFR. Patients and their physicians will be informed of any abnormal results. Two days following the administration of zoledronic acid IV or placebo, serum creatinine and a calculated creatinine clearance will be measured at the patient's facility. If the calculated creatinine clearance is <30 ml/min at the post infusion follow-up, a renal consultation will be obtained. Participants in the 1-year extension phase will also have safety labs assessed at
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month 36 (BUN, serum calcium, serum creatinine, alkaline phosphatase, albumin, and estimated GFR).

Adverse Events: We will examine all serious adverse events (hospitalizations, cancer, death). Serious Adverse Events (SAEs) will be reported to the University of Pittsburgh Institutional Review Board according to the IRB Reference Manual, Chapter 3.0, Section 3.3. Serious Adverse events will be reported to the IRB with 24 hours of notification. We will report all serious adverse events (hospitalizations, cancer, death) to Novartis Pharmaceuticals and the Data and Safety Monitoring Board. We will also capture fall data for participants as routinely collected on patients at these care facilities.

Participation and Survival Rates: Participation rates will be estimated for each study contact. Results will be calculated both for full participation (e.g., completing all procedures for the study) and for limited participation (in which only survival and clinical fragility fracture data is collected, which will be available from medical records unless the participant formally withdraws consent for the abstraction of this data). Note that after the infusion is completed, only this endpoint information would be needed for a Phase III study of clinical fracture reduction.

2.6.1 Will blood samples be obtained as part of this research study?

* yes

If Yes, address the frequency, volume per withdrawal, the total volume per visit, and the qualifications of the individual performing the procedure:
No more than 30 ml (approx. 2 tbsp.) will be drawn at each study visit, for a total of approx. 140 ml (approx. 9 tbsp.) for the entire study.

Study Flow Chart:
Name  Modified Date
Procedures & Location Table  4/12/2011 2:13 PM

2.7 Will follow-up procedures be performed specifically for research purposes?
Follow-up procedures may include phone calls, interviews, biomedical tests or other monitoring procedures.

* yes

See study flow chart in question 2.6

2.8 Does this research study involve the use of any questionnaires or survey instruments?

* yes

Upload a copy of all unpublished surveys/questionnaires. Also upload any published materials that may include questions, images, video, or sound recordings that may be especially distressing to subjects:
2.9 If subjects are also patients, will any clinical procedures that are being used for their conventional medical care also be used for research purposes?

* no

If Yes, describe the clinical procedures (and, if applicable, their frequency) that will be used for research purposes:

2.10 The blood sample question was moved to 2.6.1.

2.11 What is the total duration of the subject’s participation in this research study across all visits, including follow-up surveillance?

* Approximately 24 months

2.12 Does this research study involve any type of planned deception?
If Yes, you are required to request an alteration of the informed consent process (question 4.7)

* no

2.13 Does this research study involve the use of UPMC/Pitt protected health information that will be de-identified by an IRB approved "honest broker" system?

* no
2.14 Will protected health information from a UPMC/Pitt HIPAA covered entity be accessed for research purposes or will research data be placed in the UPMC/Pitt medical record?

* yes

Describe the medical record information that will be collected from the UPMC/Pitt HIPAA covered entity and/or the research-derived information that will be placed in the medical records.

The data to be obtained are detailed throughout section 2 and include review of history and nursing home records to assess adverse events and Minimum Data Set (MDS), questionnaires, DXA and heel ultrasound. We will collect serum samples to assess markers of bone turnover, bone mineral metabolism, and safety. The data obtained will be specifically used for research purposes. This information is also included in the HIPAA section of the informed consent documents.

2.14.1 Will protected health information from a non-UPMC/Pitt HIPAA covered entity be obtained for research purposes or will research data be placed in the non-UPMC/Pitt medical record?

* yes

If Yes, describe how the HIPAA requirements will be met:
Protected health information (PHI) from a non-UPMC/Pitt HIPAA covered entity may be obtained for research purposes by a listed investigator or co-investigator after written informed consent has been obtained from the subject or authorized representative. The PHI which may be collected is listed in the HIPAA section of the informed consent document and also in OSIRIS Section 2.14 above.

I, Susan Greenspan, certify that any member of my research team accessing, reviewing and/or recording information from medical records have completed HIPAA Researchers Privacy Requirements (Formerly RPF Module 6) training. The HIPAA certificates must be available for review if audited but do not need to be uploaded into this OSIRIS application.

* yes

2.14.2 Are you requesting a waiver of the requirement to obtain written HIPAA authorization for the collection of the PHI from a UPMC/Pitt covered entity? Note that the University of Pittsburgh IRB cannot grant a HIPAA waiver for entities outside of UPMC/Pitt.

*no

[reviewer notes-]

2.15 Does this research study involve the long-term storage (banking) of biological specimens?

* yes

2.15.1 Broadly describe the intended future use of the banked biological specimens:

Additional serum and blood will be archived for future assessment of biochemical markers. Archived samples will be labeled with unique codes and will be stored for an indefinite period of time in a locked storage room at Montefiore Hospital in the freezers belonging to the PI.
These freezers and the storage area are monitored by Vector Security alarm service. The information linking the assigned code numbers will be kept in a separate secure area at the Osteoporosis Prevention and Treatment Center. Only samples without identifiers will be shared with secondary investigators.

2.15.2 Indicate the planned length of storage of the banked biological specimens:
* Indefinitely

2.15.3 Will biological specimens be stored without identifiers or linkage codes?

* no

[reviewer notes]

2.15.4 Will subjects (including family members, if applicable) be informed of their personal results from analyses performed on their biological specimens?

* no

[reviewer notes]

2.15.4.1 Justify why the personal results will not be disclosed to the research subjects at this time. Under what conditions, if any, might personal results be disclosed to research subjects in the future?

The results of analyses performed on the stored samples are for research purposes only and will not be disclosed to participants since the results are not expected to benefit them directly or alter their course of treatment.

[reviewer notes]

2.15.4.7 Describe the procedures that will be employed to protect the confidentiality of subjects' private information associated with use of biological specimens:

Archived samples will be labeled with unique codes and will be stored for an indefinite period of time in a locked storage room at Montefiore Hospital in the freezers belonging to the PI. These freezers and the storage area are monitored by Vector Security alarm service. The information linking the assigned code numbers will be kept in a separate secure area at the Osteoporosis Prevention and Treatment Center. Only samples without identifiers will be shared with secondary investigators.

2.15.4.8 Will the banked biological specimens or data derived from them be provided with subject identifiers to any secondary investigators or external entities?

* no

2.15.4.9 Will research subjects be remunerated in the event of the future commercial development of inventions or products based on the research use of their biological specimens?

* no
2.16 Will research participants be asked to provide information about their family members or acquaintances?

* no

[reviewer notes=]

2.17 What are the main outcome variables that will be evaluated in this study?

OUTCOME VARIABLES AND MEASUREMENTS

Primary Endpoints: Primary outcomes are 1) BMD of the total hip and spine, 2) markers of bone turnover, 3) safety (adverse events and laboratory data) and feasibility, 4) participation and survival, and 5) fragility fractures through 12 months.

Secondary Endpoints: Secondary outcomes are BMD at other skeletal sites, functional and cognitive assessments, comorbidity Index and fragility fractures and survival after 12 months.

SKELETAL ASSESSMENTS

Bone Mineral Density: We will assess bone mineral density of the hip (3D hip, total hip, femoral neck, trochanter, intertrochanter), spine (PA and lateral projections), forearm, Vertebral Fracture Assessment (VFA), and total body at baseline, 6, 12 and 24 months by mobile DXA unit using a Hologic Discovery A densitometer (Hologic, Inc., Bedford, MA). We will also assess heel ultrasound to determine if differences can be seen in patients on therapy as measured using a heel ultrasound device in a frail population and correlate with results of standard DXA (screening, Months 12 and 24). We will also examine Hip Structural Analysis (HSA) by Beck and colleagues, which is a DXA derived analysis of hip geometry.

Indices of Bone Mineral Metabolism: Because bone mineral metabolism is altered with age, we will determine if the response in these indices to intravenous zoledronic acid is intervention-dependent. The monitoring of these parameters of bone mineral metabolism will further clarify our understanding of the pathophysiology of bone turnover in frail elderly women. Serum will be assayed for 25-hydroxyvitamin D2 and D3, and serum parathyroid hormone. To assess bone resorption, we will measure serum CTX and PINP. Serum will be archived and possibly assayed at a later date for the marker of bone formation, bone-specific alkaline phosphatase (BSAP), osteocalcin, and possible future assessments of bone status. Serum for indices of bone mineral metabolism and markers of bone formation will be collected at months 0, 6, 12 and 24, and batch assayed. Additional serum will be archived for future assessment of biochemical markers. Archived samples will be labeled with unique codes and will be stored for an indefinite period of time in a locked storage room at Montefiore Hospital in the freezers belonging to the PI. These freezers and the storage area are monitored by Vector Security alarm service. The Information linking the assigned code numbers will be kept in a separate secure area at the Osteoporosis Prevention and Treatment Center. Only samples without identifiers will be shared with secondary investigators.

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by obtaining the radiology report confirming the fractures.

Skeletal microarchitecture Assessments: Micro magnetic resonance imaging (MicroMRI) is a new field of clinical microscopic imaging technology that is noninvasive and has the capacity to measure trabecular bone microstructure in vivo (i.e., a virtual bone biopsy) (81, 82, 91). The system uses a patented algorithm that transforms data into a highly detailed, three-dimensional model of bone microstructure similar to that of an invasive bone biopsy (Figure 1, Appendix 3) (82, 83). A coil was installed in the University of Pittsburgh research MRI equipment for these assessments. The microMRI will assess the right distal forearm using a Sigma 1.5 Tesla scanner (GE Medical Systems, Milwaukee, WI). The reproducibility and error sources of MicroMRI have previously been described (83). The technique permits quantification of the degree to which trabecular plates (surfaces) have deteriorated to become rods (curves), a change that characterizes osteoporosis. The parameter expressing this relationship is denoted surface-to-curve ratio. It is obtained after the image data have been subjected to a cascade of processing steps so that the plates are converted to surfaces and rods to curves. Using a unique algorithm, each image voxel can then be classified as belonging to a surface or curve or junction between the two fundamental topological types (Table 2, Appendix 3). Similarly, an erosion index is determined that represents the ratio of voxels expected to decrease during resorptive bone loss, divided by those that are expected to increase.

SAFETY

Safety Labs: Safety labs will be assessed at screening, randomization, Day 2, Months 6, 12 and 24 visits and will include BUN, serum calcium, serum creatinine, liver function tests, alkaline phosphatase, albumin, TSH, 25 hydroxyvitamin D, hematocrit and hemoglobin, and estimated GFR. Patients and their physicians will be informed of any abnormal results. Two days following the administration of zoledronic acid IV or placebo, serum creatinine and a calculated creatinine clearance will be measured at the patient’s facility. If the calculated creatinine clearance is <30 ml/min at the post infusion follow-up, a renal consultation will be obtained.

Adverse Events: We will examine all serious adverse events (hospitalizations, cancer, death). Serious Adverse Events (SAEs) will be reported to the University of Pittsburgh Institutional Review Board according to the IRB Reference Manual, Chapter 3.0, Section 3.3. Serious Adverse events will be reported to the IRB with 24 hours of notification. We will report all serious adverse events (hospitalizations, cancer, death) to Novartis Pharmaceuticals and the Data and Safety Monitoring Board. We will also capture fall data for participants as routinely collected on patients at these care facilities.

Participation and Survival Rates: Participation rates will be estimated for each study contact. Results will be calculated both for full participation (e.g., completing all procedures for the study) and for limited participation (in which only survival and clinical fragility fracture data is collected, which will be available from medical records unless the participant formally withdraws consent for the abstraction of this data). Note that after the infusion is completed, only this endpoint information would be needed for a Phase III study of clinical fracture reduction.

2.18 Describe the statistical approaches that will be used to analyze the study data.

* Addressed below:

Overview: This study is intended to determine: 1) the efficacy of a single infusion of zoledronic acid in this population, assessed by BMD and markers of bone turnover; 2) the safety and feasibility of zoledronic acid in this vulnerable population and 3) estimate rates for vertebral and nonvertebral fracture reduction and survival in this cohort. To answer these questions, we will screen up to 220 women to randomize 180 women eligible into the study. Women will be randomly allocated in a 1:1 ratio to a single infusion of zoledronic acid plus daily calcium and vitamin D (group 1) or to a single infusion of zoledronic acid placebo plus daily calcium and
vitamin D (group 2). After two years, women will continue to be followed for survival and clinical fractures until all participants have been followed for two years. The primary endpoint for Specific aim 1 (efficacy) is BMD changes at 12 months. Specific aim 2 will use safety data through month 24. Rates for Specific Aim 3 will be calculated using all available data.

Adequacy of Sample Size:
Although sample size calculations often are thought to provide a unique “right” number, all such calculations are based on multiple assumptions and thus the calculation of a single number is spuriously precise (64,65). We present the estimated power of the study to answer our questions in women, given the proposed sample size for a range of endpoints. Using conservative assumptions, which should lead us to claim slightly less power than the study will actually have, our study has high power (over 95% for lumbar spine; 89% for femoral neck) to answer whether zoledronic acid has a beneficial effect on BMD using a definitive intention-to-treat analysis for Aim 1 at the end of 12 month, based on the assumptions below.

As we are studying a frail, elderly population, we assume a 30% discontinuation rate each year, which we believe is a reasonable estimate of the proportion likely to discontinue. Thus, approximately 126 of the 180 women randomized will complete year one and approximately 88 will complete year two, for an overall drop-out rate of approximately 50%.

Power statements for Aim 1 is provided for a simple two-group comparison (a non-parametric Wilcoxon rank sum test) for the change over a 12-month period to show that our study will be able to answer our questions. For the extended analysis incorporating confounders, we will use a mixed models ANOVA, which should have modestly higher power because there are potentially three measurements on an individual participant for the primary endpoint compared with two in our simplified calculations. However, calculation of a sample size for an MM-ANOVA analysis requires many additional assumptions (e.g., correlation pattern and correlations over multiple observations within a participant) with no data in this population, so our simplified approach is intended to provide a robust indication of the power of the proposed study. To propose a large multicenter study in this frail population, we need to provide clear evidence of potential efficacy in BMD and that the drug is safe in this population. We will use an intention-to-treat analysis for Aims 1 and 2. Thus, for Aim 1, we need to make an assumption about the change expected in the women not completing year one. We assume that the change will be zero. If our hypothesis is correct, this assumption reduces the anticipated difference, as drop-outs in the active group would be expected to have a BMD increase, albeit smaller than the increase among women who complete year one, while dropouts in the placebo group would be anticipated to have a decrease. Again, our assumption helps ensure that we are claiming less power than the study will likely have.

Based on published graphs, we estimate that the effect of annual zoledronic acid is about 4.5% in the lumbar spine, with a standard deviation (SD) of about 3.6%, and about 3.0% in the femoral neck with an SD of about 2.9% (43). Since elderly women have previously been shown to have smaller changes in BMD (66), we have assumed conservatively that the effect will be only 75% as large in our population, and a 0% change in the control population. Thus, the observed differences would be 2.36% (=0.7 [fraction completing 1 year] x 0.75 x 4.5%) [estimated effect in our population] + 0.3 [fraction not completing 1 year] x 0% [assumed effect in this group]) in the lumbar spine and 1.57% (=0.7 x 0.75 x 3% + 0.3 x 0%) in the femoral neck. With 90 subjects per group (all subjects included), this provides over 95% power for the effect in the lumbar spine and 89% power to detect the effect in the femoral neck. (These and all subsequent power statements are for a Wilcoxon rank sum test unless specified otherwise, with α=0.05 (2-sided) and were calculated in PASS-2002.) Thus, we have ample power for both endpoints for specific aim 1. For specific aim 2 (safety problems related to active therapy), 90 women will be exposed to Zoledronic acid. This will allow us to be 80% certain to detect a side effect that has a true incidence of 1.78%, 95% certain to observe a side effect that has a true incidence of 3.28%, and 99% certain to observe a side effect that has a true incidence of 4.99% in women.

Adequacy of Sample Size for High Resolution Wrist MRI Substudy:
Section: Section 2 - Research Design and Methods

This is a preliminary study rather than a large confirmatory one, and detailed prior data needed for a rigorous sample size computation accounting for all aspects of the statistical analysis is not possible at this time. Therefore, we base our justification on limited prior information published by others and statistical methods simpler than what we would actually sue for data analysis. Results from this study will be used for such formal sample size estimation when planning a subsequent larger trial. In addition to statistical significance, our analytic strategy for this study will involve interpretation of descriptive magnitudes of differences and associations for hypothesis generation.

A study of hypogonadal and eugonadal men (92) has shown that conservative estimates of standard deviations for 24-month change in bone volume fraction, trabecular thickness, surface-to-curve ratio and topological erosion index are 0.004, 0.7, 1.4, and 0.10, respectively. We also conservatively assume a 12-month discontinuation rate of 30%, as in the parent study. Based on this information, the proposed 30 subjects from each treatment arm will allow us to detect statistical significance of between-group differences in baseline to 12-month change in microMRI measures as small as 0.0035, 0.62, 1.24 and 0.089, respectively, with 90% power using a two-tailed test at α=0.05 level. Because variability in 12-month change tends to be less compared to 24-month change, these estimates are conservative and we expect to be able to detect even statistical significance of correlations between baseline measures of microMRI with BMD and markers of bone turnover as small as 0.35, with 80% power using a two-tailed test at α=0.05 level. Assuming the same 30% 12-month dropout rate, we will be able to detect within-group correlations as small as 0.57 between baseline to 12-month change in the same measures. Finally, a recent study (93) reported a nursing home two-year rate of 16% for nonvertebral fractures, from which we deduce >16% rate for vertebral fractures [since these will be assessed by vertebral fracture assessment (VFA) in this study and are equivalent in number (94) to more than double the rate of nonvertebral fractures (95)] and >32% for all fractures. Based on this information, we conservatively estimate to be able to detect statistical significance of hazard ratios as small as 3.59, 3.59 and 2.47 for nonvertebral, vertebral and all fractures corresponding to a unit standard deviation difference in measures of trabecular architecture with 80% power in a two-tailed test at the 0.05 level. We acknowledge these hazard ratios are large in magnitude, but reasonable for a preliminary study such as ours.

Data Analysis:

The primary analysis (Wilcoxon rank sum test) for specific aim 1 will use the intention-to-treat framework with last value carried forward (LVCF) for missing data at month 12. For participants without any followup data, the baseline value will be used. If an effect is found, one can be confident that the effect is real, and not due to potential problems in parametric or model based analyses, including violation of assumptions or inappropriate variables in the model or inappropriate assumptions when imputing missing data. Secondary analyses will use mixed models ANOVA to allow adjustment for confounders and will use available data without imputation. Depending on the pattern and reasons for missing data, we may also use multiple imputation models to confirm the primary results. The description below describes the planned efficacy analyses.

Data analysis will begin with a graphical inspection of the data. For individual participants, this will involve profile plots of BMD at the four major sites (lumbar spine, total hip, femoral neck, trochanter) to identify potential outliers. For each treatment group, this will involve scattergrams of BMD percent changes at 12 months against continuous basic demographic variables (e.g., age at consent, duration of stay in the nursing home) and boxplots of BMD percent change at 12 months against grouping variables (e.g., nursing home, severity of concomitant conditions, ambulatory status). This will allow us to gain insight into the data and to identify potential outliers. Potential outliers are checked against the source documents (or source computer files, when data are transferred automatically, e.g., BMD values) to ensure data validity. Once verified, these values are retained in all analyses.

Baseline characteristics will be summarized separately by treatment group, using standard
measures (mean/standard deviation or median/interquartile range for continuous variables; percentages for categorical variables). Standard methods will be used to compare results between treatment groups (e.g., t-test or Wilcoxon rank sum test for comparing continuous variables, Mantel-Haenszel Chi-square for ordered categorical variables, and Fisher's exact test with extensions to compare binary/unordered categorical variables).

Our first analysis will be to determine whether there are significant changes over time in the group treated with zoledronic acid. This will use a Wilcoxon rank sum test to determine whether the change at 12 months in the group treated with active drug was significantly different from the change in the group treated with placebo, using LVCF imputation for missing data. The power statements in the above section "Adequacy of Sample Size" apply directly to this analysis.

To adjust for potential confounders, we plan to use the mixed models analysis of variance (MM-ANOVA) framework to test whether there is evidence for the efficacy of zoledronic acid using all available data without imputation. The basic model would include treatment group, nursing home, ambulatory status, and time. Baseline variables, which are different between the two treatment groups (using a liberal test criterion, \( P < 0.25 \)), will be considered as additional potential confounders. These variables will be compared to the outcome variables (percent change at 12 months at lumbar spine, total hip, femoral neck, trochanter) using Spearman correlation or another standard test listed above, and any variable associated at \( P < 0.25 \) with two or more outcomes (or at \( P < 0.10 \) for any outcomes) will be considered as potential confounders and included in the model for the BMD changes. Variables significant at \( P < 0.05 \) will be retained in the final model, and interactions of all variables in the model (including nursing home and time) with treatment group will then be tested. These analyses will be repeated using LVCF imputation and the consistency of results between the two approaches will be assessed, as in our previous publication (78). If these approaches lead to qualitatively different conclusions, the effect of the LVCF procedure would be assessed using alternative imputation methods. One concern in using imputation procedures is that participants without a BMD measurement are likely to do so either because of death or significant clinical deterioration, so it is reasonable to assume that data are informatively missing. If there are substantial differences between the two groups in the proportion dropping out either because of death or because of clinical deterioration, then it will be necessary to consider how this differential discontinuation potentially biases the results of an available data analysis. If dropout rates are similar between the two groups, then it is less likely that these dropouts would bias the results of the available data analysis. We will assess whether there is evidence that changes in BMD over time are not linear (e.g., there is a sharp jump by 6 months, but not additional change at 12 months). We will do this by including a quadratic time trend in the analysis, recognizing that this is potentially overfitting the data as there are only three observations available through year one. If there is substantial evidence for non-linearity in the change in BMD over time, we will include a quadratic term in regression model.

We will assess the effect of various potential predictors of outcome in those receiving active treatment. This will include, for example, different classes of drugs (e.g., anti-convulsants, corticosteroids), different patient characteristics (e.g., cognitively impaired patients compared with patients unable to perform two or more ADLs; ambulatory status), baseline variables and change over time in baseline characteristics (geriatric comorbidity index (21)), and history of various illnesses (e.g., stroke). Significant predictors of outcome will be included in additional MM-ANOVA analyses of BMD changes to ensure validity of our conclusions. This will provide additional information in planning a definitive study to determine whether zoledronic acid reduces fractures.

The correlation model for the repeated measurements will be selected from an analysis of the data from 0 to 12 months, based on the unstructured correlation pattern and formal likelihood-ratio tests of standard correlation patterns for repeated measurements, including AR (54), compound symmetry, Toeplitz, ARIMA, Huynh-Feldt, and the unstructured correlation pattern. These analyses will assume that all treatment measurements are collected at visit
Section: Section 2 - Research Design and Methods

intervals (e.g., 6 months precisely, 12 months precisely). Analyses will be performed both with and without homogeneity of variance across time for each of the primary BMD sites (lateral spine, total hip, femoral neck, trochanter) separately by treatment group. The final correlation model will use a consensus pattern based on the results of these analyses. If an AR(54) model is ultimately selected, then time can be treated as a continuous measure with the actual interval between measurement used for the time metric, as in our previous work (67); otherwise, time needs to be treated as if all visits occurred at the scheduled time.

For relationship of BMD and markers of bone turnover, we will examine scatter plots of change in markers with change in BMD in the active treatment group and use Spearman rank correlation to assess statistical significance. Modeling in the generalized linear model framework would be used to adjust for potential confounders.

For specific aim 2, adverse events will be coded in MedDRA using the lowest level term. Preliminary reports will be prepared using the preferred term level, primary higher level term and at the primary system organ class level. We will also summarize adverse events using all higher level terms (i.e., both the primary and all secondary higher level terms to which a preferred term maps). Data will be summarized separately by treatment. For each class of event observed (preferred term or higher), the exact 95% confidence interval for the proportion of subjects with the event will be calculated. If there are sufficient events that a statistically significant result could be detected at the preferred term level or higher, formal comparisons will be done either between the active treatment group and the control group (using Fisher's exact test). As data will be available on 90 participants receiving active treatment and 90 participants receiving control treatment, then testing would be done if there are six or more events in both groups combined (which is the minimum number of events that could lead to a statistically significant result) and a difference between the groups of at least 6 events.

We will be collecting data for Specific Aim 3 to develop a definitive Phase III study looking for fracture reduction. Data on fractures and survival will be summarized using Kaplan-Meier estimates, which will be used in planning future studies. Comparisons between groups will be done using a log-rank test.

Statistical Analysis for High Resolution Wrist MRI Substudy:

SAS® version 9 (SAS Institute, Inc., Cary, North Carolina) will be used for all statistical analysis. We outline the main analytic strategy to address the specific aims of this substudy. The general issues described in detail in the parent study would apply to this substudy.

We will compare subject characteristics and the baseline measures of the two treatment groups using t-tests on Wilcoxon rank sum tests, as appropriate, for continuous variables and chi-square or Fisher's exact tests for categorical variables, as appropriate. Any significant differences will be noted to identify important architecture, we will perform analysis of covariance (ANCOVA) with baseline to 12-month change in each microMRI measure as the response variable, treatment group as the primary independent factor of interest, and baseline value of the response variable and any covariates identified as important as additional predictors. To assess robustness of the results, or as the primary analysis if a residual analysis reveals violations of assumptions for the ANCOVA, we will perform Wilcoxon rank sum tests for measures of 12-month change.

Cross-sectional associations at baseline between measures of trabecular architecture with BMD and markers of bone turnover will be quantified using Pearson or Spearman rank correlation coefficients, as appropriate, using all 60 subjects. Longitudinal correlations between baseline to 12-month change in the same measures will also be examined similarly, but within treatment group.

To examine association between trabecular architecture and future fractures independent of BMD, we will fit a Cox proportional hazards regression models using time to fracture as the
response variable censored at end of subject follow-up; each microMRI measure as the primary predictor of interest; treatment arm assignment, baseline BMD and other subject characteristics deemed important as covariates; and a possible interaction term between the microMRI measure and treatment arm assignment. Significance of the interaction term will provide evidence for differential independent associations between trabecular architecture and risk of fractures in the two treatment arms, and will allow further examination of associations within treatment arm.

2.19 Will this research be conducted in (a) a foreign country and/or (b) at a site (e.g., Navajo Nation) where the cultural background of the subject population differs substantially from that of Pittsburgh and its surrounding communities?

* no

2.21 Will this research study be conducted within a nursing home located in Pennsylvania?

* yes

2.21.1 Does this research involve a medical procedure or an experimental treatment?

* yes

2.21.2 Does the research study involve the exposure of nursing home residents to pain, injury, invasion of privacy, or ask the resident to surrender autonomy?

* yes

If Yes to either question, upload the Pennsylvania Department of Health approval letter:

Name ____________________________ Modified Date ____________________________

PA Dept of health approval 9/25/2008 12:47 PM
Section 3 - Human Subjects

3.1 What is the age range of the subject population?
65 and older

3.2 What is their gender?
* Females only - Provide a justification for limiting enrollment to only one gender.

Provide a justification if single gender selected:
Men will be excluded because they do not become postmenopausal and are less likely to become osteoporotic.

3.3 Will any racial or ethnic subgroups be explicitly excluded from participation?
* no

If Yes, identify subgroups and provide a justification:

3.4 For studies conducted in the U.S., do you expect that all subjects will be able to comprehend English?
* yes

3.5 Participation of Children: Will children less than 18 years of age be studied?
* no

If No, provide a justification for excluding children:
Children will not be included in this study because they are not frail, institutionalized elders

3.6 Does this research study involve prisoners, or is it anticipated that the research study may involve prisoners?
* no

3.7 Will pregnant women be knowingly and purposely included in this research study?
* no

3.8 Does this research study involve neonates?
3.9  **Fetal Tissues:** Does this research involve the use of fetal tissues or organs?

* no

3.10  **What is the total number of subjects to be studied at this site, including subjects to be screened for eligibility?**

Note: The number below is calculated by summing the data entered in question 3.11. Any additions or changes to the values entered in 3.11 will be reflected in 3.10.

* 300

3.11  **Identify each of the disease or condition specific subgroups (include healthy volunteers, if applicable) that will be studied.**

Click on the "Add" button and specify for each subgroup:

1) how many subjects will undergo research related procedures at this site; and

2) if applicable, how many subjects will be required to undergo screening procedures (e.g., blood work, EKG, x-rays, etc.) to establish eligibility. Do Not include subjects who will undergo preliminary telephone screening.

* Subgroup Number to undergo research procedures Number to undergo screening procedures

<table>
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<tr>
<th></th>
<th>Total Subjects (Main Study)</th>
<th>190</th>
<th>300</th>
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3.12  **Provide a statistical justification for the total number of subjects to be enrolled into this research study at the multicenter sites or this site.**

* Described below:

Subject Population:
Residents of long term care facilities, including nursing homes and assisted living facilities in the greater Pittsburgh area, will be recruited primarily from the University of Pittsburgh Medical Center (UPMC) Long Term Care Network, which comprises facilities with over 2,700 female residents. In addition, patients will be recruited from faith-based facilities, whose medical directors are also on the faculty of the Division of Geriatric Medicine at UPMC.

Co-Investigator, Dr. David Nace, is the Director for Long Term Care and a trained geriatrician on staff at the Division of Geriatric Medicine. We propose to screen up to 300 women in order to randomize up to 190 women eligible for the study, who reside in these facilities. The racial and ethnic characteristics of the proposed subject population reflect the demographics of Pittsburgh and the surrounding area and/or the patient population of the University of Pittsburgh Medical Center. We shall attempt to recruit subjects in respective proportion to
these demographics. No exclusion criteria shall be based on race, ethnicity, or HIV status.

High Resolution Wrist MRI Substudy Subjects:
Of the 180 randomized into the parent study, we will enroll 60 women (30 who have been randomized to zoledronic acid and 30 randomized to placebo) into the substudy. The study statistician will provide the research team with the allocation numbers for recruitment to ensure equal numbers of women are on active treatment and placebo.

Adequacy of Sample Size:
Although sample size calculations often are thought to provide a unique “right” number, all such calculations are based on multiple assumptions and thus the calculation of a single number is spuriously precise (64,65). We present the estimated power of the study to answer our questions in women, given the proposed sample size for a range of endpoints. Using conservative assumptions, which should lead us to claim slightly less power than the study will actually have, our study has high power (over 95% for lumbar spine; 89% for femoral neck) to answer whether zoledronic acid has a beneficial effect on BMD using a definitive intention-to-treat analysis for Aim 1 at the end of 12 month, based on the assumptions below.

As we are studying a frail, elderly population, we assume a 30% discontinuation rate each year, which we believe is a reasonable estimate of the proportion likely to discontinue. Thus, approximately 126 of the 180 women randomized will complete year one and approximately 88 will complete year two, for an overall drop-out rate of approximately 50%.

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Based on published graphs, we estimate that the effect of annual zoledronic acid is about 4.5% in the lumbar spine, with a standard deviation (SD) of about 3.6%, and about 3.0% in the femoral neck with an SD of about 2.9% (43). Since elderly women have previously been shown to have smaller changes in BMD (66), we have assumed conservatively that the effect will be only 75% as large in our population, and a 0% change in the control population. Thus, the observed differences would be 2.36% (=0.7 [fraction completing 1 year] x (0.75 x 4.5%) [estimated effect in our population] + 0.3 [fraction not completing 1 year] x 0% [assumed effect in this group]) in the lumbar spine and 1.57% (=0.7 x 0.75 x 3% + 0.3 x 0%) in the femoral neck. With 90 subjects per group (all subjects included), this provides over 95% power for the effect in the lumbar spine and 89% power to detect the effect in the femoral neck. (These and all subsequent power statements are for a Wilcoxon rank sum test unless specified otherwise, with α=0.05 (2-sided) and were calculated in PASS-2002.) Thus, we have ample power for both endpoints for specific aim 1. For specific aim 2 (safety problems related to active therapy), 90 women will be exposed to Zoledronic acid. This will allow us to be 80% certain to detect a side effect that has a true incidence of 1.78%, 95% certain to observe a
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[reviewer notes-]

3.13 Inclusion Criteria: List the specific criteria for inclusion of potential subjects.

We will include elderly women 65 years and older if they reside in a nursing home or an assisted living facility and have a known history of osteoporosis, as determined by history of an adult fragility fracture or bone mineral density criteria for osteoporosis (T-score ≤ -2.5 at the total hip, femoral neck or spine) or low bone mass (T-score ≤ -2.0 at the total hip femoral neck or spine, consistent with the National Osteoporosis Foundation Treatment guidelines) (68). If a participant's spine and or hip are not evaluable (due to surgery, calcifications, artifact in the scan area, scoliosis, etc.), they may be included in the study with a T-score of ≤ -2.0 at the forearm. Elders will be chosen without consideration of ethnic or racial background. We chose frail, institutionalized women because 70-85% of them have osteoporosis and this age group is substantially under-treated. We will include all who qualify, if they are able to weight bear or assist with transfer to chair, to ensure that the results have maximum generalizability to the nursing home population as a whole.

3.14 Exclusion Criteria: List the specific criteria for exclusion of potential subjects from participation.

Children will be excluded because they are not frail, institutionalized elders. Men will be
excluded because they do not become postmenopausal and are less likely to become osteoporotic. We will exclude institutionalized women with subacute illnesses who are not expected to survive or who will be discharged in less than 2 years. We will also exclude patients with a contraindication to bisphosphonate, such as hypocalcemia, allergy, previous adverse event (excluding gastrointestinal disorders), or currently on an oral bisphosphonate. We will exclude women with a calculated creatinine clearance of <35 ml/min (69, 70). We will exclude women scheduled for or in need of a tooth extraction as this procedure has been associated with osteonecrosis of the jaw in patients with cancer given multiple courses of high dose intravenous bisphosphonates (46-48). We will screen for these conditions by detailed history, physical exam (including dental exam), chart review, and baseline laboratory analyses, including BUN/creatinine, liver function tests, TSH, calcium, PTH, 25-hydroxyvitamin D, alkaline phosphatase and baseline calculated creatinine clearance. Participants with vitamin D levels <20 ng/mL (71, 72) will be treated with vitamin D 50,000 IU once/week for 8 weeks in addition to calcium (73, 74). Vitamin D will be rechecked and the patient will be enrolled if the vitamin D level is >20 ng/mL. If vitamin D level is still low, patients will be retreated and retested (80). Patients will be allowed to continue on certain medications known to affect bone and mineral metabolism (e.g., glucocorticoids, anticonvulsants) because their use is common in this population (75). (In our facilities, 2.9% of patients use glucocorticoids and 7.2% use anti-epileptic drugs.) In addition, women who have been treated in the past or present with osteoporosis agents, such as estrogen/progesterone, raloxifene, and calcitriol, will be allowed to participate and continue on these therapies if prescribed by their physician. However, if patients are currently on or have been on bisphosphonates for greater than 1 year in the previous 2 years prior to enrollment, they will be excluded as some bisphosphonates are long acting. Patients will be allowed to wear hip pads if prescribed by their physician. If they are on parathyroid hormone, they may participate, but will be told that monotherapy with parathyroid hormone is more beneficial than combination therapy with parathyroid hormone and alendronate, as we have previously demonstrated (76). Completely non-ambulatory patients who cannot weight bear to assist with transfer to a chair will be excluded. High Resolution Wrist MRI Substudy Inclusion/Exclusion: Inclusion and exclusion will be similar to the parent study. However, subjects recruited into the substudy must be cognitively intact due to the need for cooperation during the MRI procedure. Additional exclusion criteria mandated by considerations of incompatibility for MRI include carriers of specific cardiac pacemakers, subjects with ferromagnetic implants, subjects who are claustrophobic, subjects who have sustained a right wrist fracture or who have a body mass index >30.

3.15 Will HIV serostatus be evaluated specifically for the purpose of participation in this research study?

* no

If Yes, provide a justification:
4.1 Select all recruitment methods to be used to identify potential subjects:

**Advertisements**

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**Recruitment Letters and Scripts**

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<tr>
<td>Recruitment letter</td>
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</table>

4.2 Provide a detailed description of your recruitment methods, including identifying and initiating contact with participants:

Recruitment Methods and Consent Procedures:

Prior to study initiation, IRB approval will be obtained through the University of Pittsburgh. In addition, approval will be obtained from the Pennsylvania Department of Health, in accordance with pertinent state regulations. Dr. David Nace, a co-investigator, has expertise in working with the state Division of Nursing Home Licensure to facilitate this process. Recruitment will occur during the first 2.5 years of the grant cycle. Dr. Nace has discussed the clinical trial and research objectives with the medical directors of the participating study facilities. Depending on each institution's policy, the protocol may also be presented to the medical care committee,
owners, or governing body. After official approval is obtained, the protocol will be presented to the facility’s staff. Our staff will then present an in-service on osteoporosis risk factors, diagnosis, prevention measures, and study details. After the medical directors have provided approval and primary care physicians have been informed about the study, we will recruit subjects from the care facilities with the help of the nursing home or assisted living facility staff.

Cognitive impairment is highly prevalent in assisted living and nursing home settings and is considered when obtaining consent for screening. Competence will be assessed with a several stage process. Each potential participant will be reviewed with the nursing supervisor and/or attending physician to determine if the patient is able to personally provide informed consent. With a witness present (family or nursing home staff member not affiliated with the study), after a brief introduction, the candidate will be asked what they are being asked to decide. If they cannot respond, they will be considered incompetent for this purpose and the care facility will send their legally responsible party (next of kin or guardian as identified by the facility’s records) a letter describing the study and informing them that a designated staff member of the nursing home or assisted living facility will be contacting them regarding the candidate’s possible participation. They may decline to be contacted by returning an enclosed postcard to the nursing home or assisted living facility that will be included with the letter. A contact number for the Osteoporosis Prevention and Treatment Center will also be provided so that they may contact the research study team directly if they wish to do so. We will discuss the study with the patient’s physician and any other pertinent clinician involved in the resident’s care.

Each nursing home will designate a staff member to approach potential participants to tell them about the study and ascertain interest. If the potential participant expresses interest, the facility staff will ask their permission for the study coordinator to talk to them about the details of the study and her verbal consent to be contacted by the investigators will be documented in her record. If the potential participant agrees, the study coordinator or study co-investigator will discuss the nature, purpose, and design of the study with prospective subjects. Subjects will be consented first for screening procedures by the study coordinator or co-investigator using the screening consent document, and those eligible for the study will be consented for study procedures by a physician investigator using the separate study consent document. Potential risks and benefits will be described orally and in writing. Those consenting to participate for screening will be required to sign an informed consent form describing the nature, purpose, design and risk/benefit ratio for the screening, and the certification of informed consent statement for screening will be signed by the study coordinator or a study co-investigator. During the recruitment and screening phase, the study coordinator will visit each of the participating nursing homes once per week.

Recruitment will also be through social and education events for patients and their families, which will be hosted by the care facilities. These events will be advertised by flyers posted at the care facilities and the flyers may also be mailed to the billing address for residents by the care facilities. Notice of these events may also be advertised in the care facility newsletters. Research staff will be available to talk about osteoporosis and answer questions at these events, which will also include games such as "osteoporosis bingo" to increase awareness about osteoporosis and this research study. Small prizes will be awarded to game and raffle winners (approximate value ranging from $1-$5) and small promotional items will be given to all attendees (such as buttons, pens, nail files, notepads, etc. with a value of under $3).

To increase awareness about the research study among physicians treating patients at these care facilities, we will be sending physician-to-physician letters describing the study.

Those eligible for the study will undergo a separate informed consent for the study procedures. The nature, purpose, and design of the study will be discussed orally and in writing by the PI, research nurse, or research assistants. The risks involved also will be described in detail. If interested in participating, written informed consent will be obtained and assent will be sought from those unable to give informed consent. We will discuss the study with the patient’s attending physician and any other pertinent clinician involved in the
resident's care. For all participants with cognitive impairment, as determined by the primary care provider, we will discuss the study with a designated family member. If assent is given by the participant, we will obtain informed consent from the legal guardian or designated family member. The consent form will be filed with the participant's medical record. In addition, the participant and guardian will be provided with a copy of the consent form, which may be kept in the nursing home or assisted living facility.

Addendum consent forms will be used to inform participants already enrolled of any new information related to the study. Consent will be obtained in the same manner as described above for cognitively intact and cognitively impaired participants. The new information will be discussed orally and in writing by the PI, research nurse, or research assistants and the certification of informed consent statement for the addendum will be signed by the study coordinator or a study co-investigator. A copy of the signed consent addendum will be filed with the participant's medical record. In addition, the participant and guardian will be provided with a copy of the consent form addendum, which may be kept in the nursing home or assisted living facility. Addendum consent form #5 will be used to provide subjects with information on the 1-year extension phase, and those subjects who choose to participate in the extension phase will enroll in the extension by signing ICF Addendum #5. Consent with Addendum #5 will be obtained in the same manner as described above for cognitively intact and cognitively impaired participants.

A letter with information about the study will also be sent by the care facilities to residents and their families to increase awareness that the study is open for recruitment, stating that they may be contacted by the study investigators or study team to determine their interest in participation. They may decline to be contacted by returning an enclosed stamped postcard that will be included with the letter or by calling the telephone contact number provided. Neither the PI nor research study staff will contact any potential subject for at least 2 weeks following the mailing of the letters to allow time for response. Advertising flyers will also be posted at the care facilities, and ads will be placed in care facility newsletters. Subjects enrolled in the parent study may also be eligible for the high resolution wrist MRI substudy for which they will undergo a separate informed consent. The PI, study coordinator, or study co-investigator will discuss the nature, purpose, and design of the substudy with prospective subjects. Potential risks and benefits of the substudy will be described orally and in writing. Those consenting to participate in the substudy will be required to sign the substudy informed consent document prior to undergoing any substudy procedures and the certification of informed consent statement will be signed by the PI, study coordinator, or study co-investigator.

4.6 Are you requesting a waiver to document informed consent for any or all participants, for any or all procedures? (e.g., a verbal or computerized consent script will be used, but the subjects will not be required to sign a written informed consent document. This is not a waiver to obtain consent.

* no

4.7 Are you requesting a waiver to obtain informed consent or an alteration of the informed consent process for any of the following?

* no
4.7.1 If Yes, select the reason(s) for your request:
There are no items to display

4.8 Are you requesting an exception to the requirement to obtain informed consent for research involving the evaluation of an 'emergency' procedure?

Note: This exception allows research on life-threatening conditions for which available treatments are unproven or unsatisfactory and where it is not possible to obtain informed consent.

* no

4.9 Upload all written informed consent documents.

Draft Consent Forms for editing:

<table>
<thead>
<tr>
<th>Name</th>
<th>Modified Date</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
<tr>
<td>Addendum ICF #5 (1-yr extension phase)</td>
<td>1/27/2011 11:55 AM</td>
</tr>
<tr>
<td>Addendum ICF#4</td>
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<tr>
<td>Main Study ICF</td>
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<tr>
<td>Study ICF</td>
<td>12/14/2010 12:32 PM</td>
</tr>
</tbody>
</table>

Approved Consent Form(s):

<table>
<thead>
<tr>
<th>Name</th>
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<tr>
<td>Addendum ICF#4</td>
<td>12/14/2010 12:39 PM</td>
</tr>
<tr>
<td>Addendum ICF #5 (1-yr extension phase)</td>
<td>1/27/2011 11:55 AM</td>
</tr>
<tr>
<td>Addendum ICF#3</td>
<td>12/14/2010 12:31 PM</td>
</tr>
</tbody>
</table>
4.10 Will all potential adult subjects be capable of providing direct consent for study participation?

* No

Indicate why direct consent is not possible: Participants may be decisionally impaired and unable to provide written informed consent, however their assent will be obtained and written informed consent will be obtained from their authorized representative.

4.10.1 Provide a justification for the inclusion of adult subjects who are unable to provide direct consent for study participation.

We are very sensitive to research in cognitively impaired patients but feel strongly about their inclusion as well as our capability to handle their inclusion for a variety of reasons:

a. Prevalence of Cognitive Impairment in the Nursing Home: Because 50-75% of patients in some long term care facilities have some cognitive impairment, omission of these patients would significantly limit the inclusion of the cohort proposed for the NIH-funded study as well as the generalizability of these findings.

b. Qualifications of Investigators: Dr. Greenspan, the PI, Dr. Resnick, Chief of Geriatrics and Dr. Nace, co-investigator, are all board certified geriatricians. In addition to Drs. Resnick and Greenspan who have previously done research in nursing home patients looking at osteoporosis, falls and fractures, Dr. Nace is the Director of Long Term Care at the University of Pittsburgh Medical Center and has a solid track record in clinical research, program development, education and quality of life in the long term care setting. He has been collaborating with studies in the nursing home setting for the past 10 years and includes studies that have examined end of life, promoting long term care vaccines, quality enhancement and education in the nursing home, leadership training in the nursing home, treatment of nursing home acquired pneumonia and long term care medication error reduction.

c. NIH Outlook: The NIH Consensus Development Conference on Osteoporosis: Prevention, Diagnosis and Therapy in March 2000, identified frail nursing home residents as one of the 5 critical areas that need immediate attention [Anonymous. NIH consensus declares osteoporosis a major public health issue. Osteoporosis Report 2000;16:1]. There are data suggesting that cognitive impairment may be an independent and significant risk factor for fractures and bone loss. These patients may respond differently to treatment. The new NIH roadmap emphasizes more clinically relevant studies. We hope to examine how cognitive impairment affects the response to therapy and predicts outcome. Most importantly, these patients comprise the group that potentially needs an answer to the question of efficacy and safety because of the greater increase in morbidity, mortality and neglect that they suffer.

4.10.2 Specify the criteria used to determine that a potential adult subject is not able to provide direct consent for participation and identify who will be responsible for that determination.

Cognitive impairment is highly prevalent in assisted living and nursing home settings and is considered when obtaining consent for screening. Competence will be assessed with a several stage process. Each potential participant will be reviewed with the nursing supervisor and/or attending physician to determine if the patient is able to personally provide informed consent. With a witness present (family or nursing home staff member not affiliated with the study), after a brief introduction, the candidate will be asked what they are being asked to decide. If they cannot respond, they will be considered incompetent for this purpose and the care facility will send their legally responsible party (next of kin or guardian as identified by the facility’s records) a letter describing the study and informing them that a designated staff member of the nursing home or assisted living facility will be contacting them regarding the candidate’s
possible participation. They may decline to be contacted by returning an enclosed postcard to the nursing home or assisted living facility that will be included with the letter. A contact number for the Osteoporosis Prevention and Treatment Center will also be provided so that they may contact the research study team directly if they wish to do so. We will discuss the study with the patient's physician and any other pertinent clinician involved in the resident's care.

4.10.3 Will you obtain the potential adult subject's assent for study participation?

* yes

If No, provide a justification for not obtaining assent:

4.10.4 Identify who will provide proxy consent for the participation of the decisionally impaired adult:

For all participants with cognitive impairment, as determined by the primary care provider, we will discuss the study with the designated legally responsible party (the adult documented to have made decisions for the subject in prior health care settings). If consent is given by the participant, we will obtain informed consent from the legally responsible party. The consent form will be filed with the participant's medical record. In addition, the participant and proxy will be provided with a copy of the consent form, which may be kept in the nursing home or assisted living facility.

[Reviewer notes -]

4.11 At what point will you obtain the informed consent of potential research subjects or their authorized representative?

Prior to performing any of the screening procedures

4.11.2 Taking into account the nature of the study and subject population, indicate how the research team will ensure that subjects have sufficient time to decide whether to participate in this study. In addition, describe the steps that will be taken to minimize the possibility of coercion or undue influence.

Participation is voluntary and participants may withdraw their consent for participation at any time. Potential participants may review the consent forms in advance of meeting with study staff to discuss the study, and the study staff and PI are available to answer any questions they may have. The PI and research staff are also available to family members and legal representatives to discuss the study, consent forms, and any questions they may have about the study. Participants are given time to review the consents at their leisure as the study coordinators visit the care facilities weekly to follow-up with patients who have expressed interest in participating.

Each nursing home will designate a staff member to approach potential participants to tell them about the study and ascertain interest. If the potential participant expresses interest, the facility staff will ask their permission for the study coordinator to talk to them about the details of the study and her verbal consent to be contacted by the investigators will be documented in her record. If the potential participant agrees, the study coordinator or study co-investigator will discuss the nature, purpose, and design of the study with prospective subjects. Subjects will be consented first for screening procedures by the study coordinator or co-investigator using the screening consent document, and those eligible for the study will be consented for study procedures by a physician investigator using the separate study consent document. Potential risks and benefits will be described orally and in writing. Those consenting to participate for screening will be required to sign an informed consent form describing the nature, purpose, design and risk/benefit ratio for the screening, and the certification of
Informed consent statement for screening will be signed by the study coordinator or a study co-investigator. During the recruitment and screening phase, the study coordinator will visit each of the participating nursing homes once per week.

Those eligible for the study will undergo a separate informed consent for the study procedures. The nature, purpose, and design of the study will be discussed orally and in writing by the PI, research nurse, or research assistants. The risks involved also will be described in detail. If interested in participating, written informed consent will be obtained and assent will be sought from those unable to give informed consent. We will discuss the study with the patient’s attending physician and any other pertinent clinician involved in the resident’s care. For all participants with cognitive impairment, as determined by the primary care provider, we will discuss the study with a designated family member. If assent is given by the participant, we will obtain informed consent from the legal guardian or designated family member. The consent form will be filed with the participant’s medical record. In addition, the participant and guardian will be provided with a copy of the consent form, which may be kept in the nursing home or assisted living facility.

4.12 Describe the process that you will employ to ensure the subjects are fully informed about this research study.

* Addressed below:
This description must include the following elements:

- who from the research team will be involved in the consent process (both the discussion and documentation);
- person who will provide consent or permission;
- information communicated; and
- any waiting period between informing the prospective participant about the study and obtaining consent

Each nursing home will designate a staff member to approach potential participants to tell them about the study and ascertain interest. If the potential participant expresses interest, the facility staff will ask their permission for the study coordinator to talk to them about the details of the study and her verbal consent to be contacted by the investigators will be documented in her record. If the potential participant agrees, the study coordinator or study co-investigator will discuss the nature, purpose, and design of the study with prospective subjects. Subjects will be consented first for screening procedures by the study coordinator or co-investigator using the screening consent document, and those eligible for the study will be consented for study procedures by a physician investigator using the separate study consent document. Potential risks and benefits will be described orally and in writing. Those consenting to participate for screening will be required to sign an informed consent form describing the nature, purpose, design and risk/benefit ratio for the screening, and the certification of informed consent statement for screening will be signed by the study coordinator or a study co-investigator. During the recruitment and screening phase, the study coordinator will visit each of the participating nursing homes once per week.

Cognitive impairment is highly prevalent in assisted living and nursing home settings and is considered when obtaining consent for screening. Competence will be assessed with a several stage process. Each potential participant will be reviewed with the nursing supervisor and/or attending physician to determine if the patient is able to personally provide informed consent. With a witnessed present (family or nursing home staff member not affiliated with the study), after a brief introduction, the candidate will be asked what they are being asked to decide. If they cannot respond, they will be considered incompetent for this purpose and the care facility will send their legally responsible party (next of kin or guardian as identified by the facility’s
records) a letter describing the study and informing them that a designated staff member of the nursing home or assisted living facility will be contacting them regarding the candidate’s possible participation. They may decline to be contacted by returning an enclosed postcard to the nursing home or assisted living facility that will be included with the letter. A contact number for the Osteoporosis Prevention and Treatment Center will also be provided so that they may contact the research study team directly if they wish to do so. We will discuss the study with the patient’s physician and any other pertinent clinician involved in the resident’s care.

4.13 Are you requesting an exception to either IRB policy related to the informed consent process?

- For studies involving a drug, device or surgical procedures, a **listed physician** investigator is required to obtain the written informed consent unless an exception to this policy has been approved by the IRB.
- For all other studies, a **listed** investigator is required to obtain consent (Note: In order to request an exception to this policy, the study must be minimal risk)

* no

If Yes, provide a justification and describe the qualifications of the individual who will obtain consent:

4.14 Will you inform research subjects about the outcome of this research study following its completion?

* yes

If Yes, describe the process to inform subjects of the results:
Subjects will receive notification by mail as to which study group they were assigned.
### 5.1 Describe potential risks (physical, psychological, social, legal, economic or other) associated with screening procedures, research interventions/interactions, and follow-up/monitoring procedures performed specifically for this study:

<table>
<thead>
<tr>
<th>Research Activity:</th>
<th>(see previous sections for risks related to study drug / placebo, calcium and vitamin D supplements, radiation exposure from DXA scans, blood draw, walking and balance tests, heel ultrasound, and high resolution wrist MRI for the substudy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common Risks:</td>
<td>No Value Entered</td>
</tr>
<tr>
<td>Infrequent Risks:</td>
<td>No Value Entered</td>
</tr>
<tr>
<td>Other Risks:</td>
<td>No Value Entered</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Research Activity:</th>
<th>Blood Draw</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common Risks:</td>
<td>Screening Procedures: The risks and discomforts of having blood drawn include the possibility of pain, bruising, or soreness at the site of the blood draw and an occasional feeling of lightheadedness (occurs in 1-25% of people, or 1-25 people out of 100).</td>
</tr>
<tr>
<td>Infrequent Risks:</td>
<td>No Value Entered</td>
</tr>
<tr>
<td>Other Risks:</td>
<td>Screening Procedures: Rarely, infection at the site of the blood draw (occurs in less than 1%, or less than 1 out of 100 people).</td>
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</table>

<table>
<thead>
<tr>
<th>Research Activity:</th>
<th>Blood Draw:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common Risks:</td>
<td>Experimental Interventions: Some common risks may include pain, bleeding, and the possibility of bruising at the site of the blood draw or the feeling of lightheadedness (occurs in 1-25%, or 1-25 people out of 100), and rarely, fainting or infection at the site of the blood draw (occurs in less than 1%, or less than 1 out of 100 people).</td>
</tr>
<tr>
<td>Infrequent Risks:</td>
<td>No Value Entered</td>
</tr>
<tr>
<td>Other Risks:</td>
<td>No Value Entered</td>
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<table>
<thead>
<tr>
<th>Research Activity:</th>
<th>Calcium and vitamin D supplements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common Risks:</td>
<td>Experimental Interventions: Participants will take 1200 mg of calcium daily and 800 IU of vitamin D daily. Mild constipation from the calcium supplement occurs commonly in 1%-25%, or 1-25 people out of 100). This may be eliminated by adding dietary fiber. There are no known side effect for vitamin D when it is taken within the recommended daily allowance of 400-800 IU.</td>
</tr>
<tr>
<td>Infrequent Risks:</td>
<td>No Value Entered</td>
</tr>
<tr>
<td>Other Risks:</td>
<td>No Value Entered</td>
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<table>
<thead>
<tr>
<th>Research Activity:</th>
<th>DXA Scan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common Risks:</td>
<td>No Value Entered</td>
</tr>
<tr>
<td>Infrequent Risks:</td>
<td>No Value Entered</td>
</tr>
<tr>
<td>Other Risks:</td>
<td>Screening Procedures: Participation in this research study screening will involve exposure to radiation from the DXA scans. DXA Scans: Participation in this research study screening will involve exposure to radiation from the dual-energy x-ray absorpti Experimental Interventions: Participation in this research study will involve exposure to radiation from the DXA studies (PA and lateral spine, total hip, forearm, VFA, total body, and 3D hip). If a participant completes all of...</td>
</tr>
</tbody>
</table>
these DXA studies, as outlined in the protocol, the total radiation dose to the spine will be about 236 mrem (an mrem is a unit of radiation). The radiation dose to the hip will be about 380 mrem, the radiation dose to the wrist will be 20 mrem, and the radiation to the total body would be 4 mrem. For comparison, these radiation doses are a very small fraction of the maximum annual single organ radiation dose (50,000 mrem) and maximum annual whole body radiation dose (5000 mrem) permitted by federal regulation to all radiation workers. There is no minimum level of radiation exposure that is recognized as being totally free of the risk of causing genetic mutations or cancer. However, the risk associated with the amount of radiation exposure received from participation in this study is considered to be low and comparable to everyday risks. Participation in the 1-year extension phase of this research study will involve exposure to radiation from the DXA studies (PA and lateral spine, hip, total hip, wrist, VFA, and total body) from an additional DXA study at Month 36. If a participant completes the 1-year extension phase, as outlined in the protocol, the total radiation dose to the spine from this additional Month 36 visit will be about 59 mrem (an mrem is a unit of radiation), the radiation dose to the hip will be about 95 mrem, the radiation dose to the wrist will be 5 mrem, and the radiation to the total body would be 1 mrem.

<table>
<thead>
<tr>
<th>Research Activity:</th>
<th>Heel Ultrasound</th>
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<td>Common Risks:</td>
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</tr>
<tr>
<td>Infrequent Risks:</td>
<td>No Value Entered</td>
</tr>
<tr>
<td>Other Risks:</td>
<td>Experimental Interventions: There is no known risk from calcaneal ultrasound.</td>
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</table>

<table>
<thead>
<tr>
<th>Research Activity:</th>
<th>High Resolution Wrist MRI (Substudy Participants Only)</th>
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</thead>
<tbody>
<tr>
<td>Common Risks:</td>
<td>Experimental Interventions: Participation in the microMRI study will involve MRI studies of the wrist. There are no known health risks associated with exposure to magnetic fields during the MRI. However, there is the potential risk of the magnetic field of the scanner attracting metal objects toward the magnet. The MRI scanner will make loud knocking noises that could cause ear discomfort is some people. Some subjects may feel discomfort from lying on the hard surface of the scanner bed for approximately 30 minutes. Some people may feel uncomfortable (claustrophobic) in the small space inside the MRI scanner.</td>
</tr>
<tr>
<td>Infrequent Risks:</td>
<td>No Value Entered</td>
</tr>
<tr>
<td>Other Risks:</td>
<td>No Value Entered</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Research Activity:</th>
<th>Intravenous Zoledronic Acid (Reclast®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common Risks:</td>
<td>Experimental Interventions: Common side effects (occurs in 10-25% of people, or 10-25 people out of 100) are joint pain, fever, anemia, nausea, and flu-like symptoms. Between 10 to 20% of persons who receive zoledronic acid by vein experience mild flu-like symptoms that include a small rise in body temperature in the 24-48 hours after receiving the first dose.</td>
</tr>
<tr>
<td>Infrequent Risks:</td>
<td>Experimental Interventions: Infrequent side effects (occurs in 1-10%, or 1-10 people out of 100) are back pain, fatigue, skeletal pain, leg pain, muscle pain or tenderness, headache, reduced levels of calcium, phosphorus and/or potassium levels in your blood, temporary mild increases in white blood cells and platelets, and conjunctivitis.</td>
</tr>
</tbody>
</table>
Section: Section 5 - Potential Risks and Benefits

Other Risks: Experimental Interventions: Rare side effects (occurs in less than 1%, or in less than 1 person out of 100) include harm to kidney function and eye pain. In advanced cancer patients receiving, among other anticancer treatments, a bisphosphonate (such as pamidronate or zoledronic acid/Zometa), there have been reports of a condition known as osteonecrosis of the jaws. This means a portion of the jawbone becomes permanently damaged, may be painful, and may require dental treatment or removal of the damaged area. This condition occurs rarely (occurs in less than 1% of people, or in less than 1 person out of 100), and may follow tooth extraction. Because many treatments (such as chemotherapy, corticosteroids and radiation) or dental procedures and medical conditions that can increase the risk of osteonecrosis of the jaws may be administered or occur concomitantly with bisphosphonate therapy, it is not clear if the reported cases of osteonecrosis of the jaws are related to the use of bisphosphonates or to these other treatments, medical conditions or dental procedures. In a recent study of post-menopausal women with osteoporosis, a small number of patients experienced atrial fibrillation. The rate of patients receiving medical treatment for this condition was higher in those taking zoledronic acid (approx. 13 per 1000 patients) than in those taking placebo (approx. 5 per 1000). More research is needed before the significance of this finding becomes clear. In addition, subjects may also experience redness, bruising, warmth, bleeding or rash at the infusion site. These reactions are usually mild and last a short time. The Food and Drug Administration (FDA) issued the following new information describing the risk of atypical fractures of the thigh, known as subtrochanteric and diaphyseal femur fractures, in patients who take bisphosphonates for osteoporosis: Bisphosphonates are a class of medicines that can be effective at preventing or slowing the loss of bone mass (osteoporosis) in postmenopausal women, thus reducing the risk of common osteoporotic bone fracture. Osteoporotic fractures can result in pain, hospitalization, and surgery. Atypical subtrochanteric femur fractures are fractures in the bone just below the hip joint. Diaphyseal femur fractures occur in the long part of the thigh bone. These fractures are very uncommon and appear to account for less than 1% (less than 1 person out of 100) of all hip and femur fractures overall. Although it is not clear if bisphosphonates are the cause, these unusual femur fractures have been predominately reported in patients taking bisphosphonates. Although the optimal duration of bisphosphonate use for osteoporosis is unknown, these atypical fractures may be related to long-term bisphosphonate use. The FDA will require a new Limitations of Use statement in the Indications and Usage section of the labels for these drugs. This statement will describe the uncertainty of the optimal duration of use of bisphosphonates for the treatment and/or prevention of osteoporosis.

Research Activity: Placebo

Common Risks: No Value Entered

Infrequent Risks: No Value Entered

Other Risks: Experimental Interventions: Subjects in the placebo group will have the same risks as described in this risks section except for those associated with zoledronic acid (Reclast®) as described above. There is a potential risk for bone loss in not receiving the study drug, however all participants will receive calcium and vitamin D supplements which have been shown to reduce bone loss although not as effectively as bisphosphonates (zoledronic acid [Reclast®] is a bisphosphonate).
### 5.1.1 Describe the steps that will be taken to prevent or to minimize the severity of the potential risks:

**Screening Procedures:**

**Walking and Balance Tests:**
The study coordinator is trained to intervene to prevent a fall from and happening. Participants can decline to do any of the balance and walking tests that they do not want to do or that they feel is too painful. All tests will be done in a private room except the walking test, which will be done in a cleared hallway to avoid any breach of confidentiality (to protect participant privacy).

Following serum sampling, a registered nurse, physician assistant, or phlebotomist will observe and monitor subjects for lightheadedness or adverse reactions such as bleeding, bruising, or rash at the site from which blood was drawn.

**Experimental Interventions:**

Contraindication to intravenous zoledronic acid will be determined by our screening history, physical exam, dental exam, and discussion with the primary care providers. Confidentiality will be maintained through our computer-oriented data coding system, which will use study identification numbers. Test results of individual participants will be analyzed, reported, and discussed with the study team in reference to the study identification number. When data are discussed with the participants on an individual basis, only that participant's data will be discussed. When the participant requests further information, the general findings and conclusions of the study will be described after the study is complete. The PI will maintain complete control over all data. Modifications to the research protocol will be implemented only after IRB approval is received and all participants will sign the newly approved informed consent form.

Between 10 to 20% of persons who receive zoledronic acid by vein experience mild flu-like symptoms that include a small rise in body temperature in the 24-48 hours after receiving the first dose. The temporary fever and flu-like symptoms can be treated with acetaminophen, just like treatment for flu. Participants will be provided with acetaminophen to be taken every 6 hours, as needed, for 72 hours following IV administration of zoledronic acid. In managing
these symptoms, it is important to drink adequate fluids to avoid dehydration.

Treatment with zoledronic acid is not advised or must be used cautiously in people with any of the following conditions: 1) previous history of allergic reaction or sensitivity to bisphosphonates, 2) severe kidney and heart disease, and 3) preexisting anemia, decreased white blood cell count or clotting problems. The study doctor will discuss the importance of these risks with participants.

If we find that a participant has significant bone loss during the study, they will be informed and may be discontinued from the blinded portion of the study and appropriate treatment options will be discussed with them. Participants will be allowed to continue in the study for follow-up visits on a therapy chosen by them and their physician. It is possible that some study participants in the placebo arm could experience bone loss, although calcium and vitamin D have been shown to reduce hip and other nonvertebral fractures in nursing home patients (28). If the BMD operator notes a decrease in BMD of >6.4% at the hip or spine between two consecutive 6 month visits based on the least significant change in a Hologic machine in this population (78, 79), the participant will be asked to repeat the DXA scan to determine whether positioning errors led to a false decrease. If the initial result is confirmed on follow-up, she will be informed and appropriate treatment options will be discussed. She may be discontinued from the blinded portion of the study, but will continue in the study for follow-up visits on a therapy chosen by her and her physician. We will ask the subject’s permission to send the DXA results to her personal physician for follow-up treatment; if the subject is cognitively impaired, we will ask the subject’s legal guardian for permission to send the DXA results to the subject’s personal physician for follow-up treatment.

Following serum sampling, a registered nurse, physician assistant, or phlebotomist will observe and monitor subjects for lightheadedness or adverse reactions such as bleeding, bruising, or rash at the site from which blood was drawn. No more than 30 ml (approx. 2 tbsp.) will be drawn at each study visit, for a total of approximately 140 ml (approx. 9 tbsp.) for the entire study. If repeat testing is necessary, this would increase the total amount of blood drawn over the entire study; however no more than 30 ml (approx. 2 tbsp.) will be drawn as a repeat test for each study visit.

High Resolution Wrist MRI Substudy: To reduce the risk of a metal object flying toward the magnet, all subjects must remove all metal from their bodies, including jewelry, watches, keys, hair or safety pins, and clothing with metal. No metal objects will be brought into the magnet room at any time. In addition, subjects are screened to exclude those not compatible for MRI procedures (subjects with cardiac pacemakers, ferromagnetic implants, claustrophobia). Participants will be told about the potential loud noise from the scanner. To block out the noise from the scanner, participants will be provided with protective ear plugs. Participants will also be informed about the potential discomfort of lying on a hard surface for approximately 30 minutes. Every attempt will be made to ensure comfort while lying on the table.

Follow up Procedures:

(same as in previous sections 5.1.2. and 5.2.2)

5.2 What steps will be taken in the event that a clinically significant, unexpected disease or condition is identified during the conduct of the study?

* Addressed below:

Patients and their physicians will be informed of any abnormal results.
5.3 All the risk questions (screening, intervention/interaction, follow-up) have been merged into one question (5.1).

[reviewer notes-]

5.4 Do any of the research procedures pose a physical or clinically significant psychological risk to women who are or may be pregnant or to a fetus?

* no

[reviewer notes-]

5.5 Do any of the research procedures pose a potential risk of causing genetic mutations that could lead to birth defects?

* No

[reviewer notes-]

5.6 Are there any alternative procedures or courses of treatment which may be of benefit to the subject if they choose not to participate in this study?

* Yes - Describe below:

If Yes, describe in detail:
Potential subjects may choose not to participate and either continue their present health treatment plan or discuss alternative therapies with their physician. DXA scans of various body regions (e.g. the spine, hip, heel, wrist, finger, total body) are available outside of study participation for the diagnosis and evaluation of osteoporosis.

[reviewer notes-]

5.7 Describe the specific endpoints (e.g., adverse reactions/events, failure to demonstrate effectiveness, disease progression) or other circumstances (e.g., subject's failure to follow study procedures) that will result in discontinuing a subject's participation?

* Describe below:

It is possible that some study participants in the placebo arm could experience bone loss, although calcium and vitamin D have been shown to reduce hip and other nonvertebral fractures in nursing home patients (28). If the BMD operator notes a decrease in BMD of >6.4% at the hip or spine between two consecutive 6 month visits based on the least significant change in a Hologic machine in this population (78, 79), the participant will be asked to repeat the DXA scan to determine whether positioning errors led to a false decrease. If the initial result is confirmed on follow-up, she will be informed and appropriate treatment options will be discussed. She may be discontinued from the blinded portion of the study, but will continue in the study for follow-up visits on a therapy chosen by her and her physician. We will ask the subject’s permission to send the DXA results to her personal physician for follow-up treatment; if the subject is cognitively impaired, we will ask the subject’s legal guardian for permission to send the DXA results to the subject’s personal physician for follow-up treatment.
5.8 Will any individuals other than the investigators/research staff involved in the conduct of this research study and authorized representatives of the University Research Conduct and Compliance Office (RCCO) be permitted access to research data/documents (including medical record information) associated with the conduct of this research study?

* yes

5.8.1 Identify the 'external' persons or entity who may have access to research data/documents and the purpose of this access:

In unusual cases, the investigators may be required to release identifiable information, which may include identifiable medical information, related to participation in this research study in response to an order from a court of law. Authorized representatives of the sponsors of this research study may review identifiable information related to participation in this research study for the purpose of monitoring the accuracy and completeness of the research data, performing required scientific analyses of the research data, and monitoring participant safety. Information related to participant adverse events will also be monitored by Novartis Pharmaceuticals Corp. which is providing the study drug, and by the study data and safety monitoring board (DSMB). Authorized representative of the U. S. Food and Drug Administration (FDA) may review and/or obtain identifiable information for the purpose of monitoring the accuracy of the research data. Authorized representatives of UPMC hospitals or other affiliated health care providers may have access to identifiable information for the purpose of (1) fulfilling orders, made by the investigators, for hospital and health care services (e.g., laboratory tests, diagnostic procedures) associated with research study participation; (2) addressing correct payment for tests and procedures ordered by the investigators; and/or (3) for internal hospital operations (i.e. quality assurance). Authorized representatives of the Pennsylvania Department of Health may review and/or obtain identifiable information, which may include identifiable medical information, related to participation in this research study for the purposes of monitoring the appropriate conduct of this research study. Pennsylvania Code specifies that experimental research or treatment carried out in a nursing home must be approved by the Pennsylvania Department of Health. High resolution wrist MRI scans will be sent to MicroMRI, Inc. for analysis without identifiers.

5.8.2 Will these 'external' persons or entity have access to identifiable research data/documents?

* Yes - Describe below:

If Yes, describe how they will protect the confidentiality of the research data: While the external persons/entities described above understand the importance of maintaining the confidentiality of identifiable research and medical information, we cannot guarantee the confidentiality of this information after it has been obtained by them. In order to maintain confidentiality when external persons have access to research data, the research data will be viewed in a private, secure room in an area accessible only to staff.

5.9 Has or will a Federal Certificate of Confidentiality be obtained for this research study?

* no

5.10 Question has been moved to 5.17
Question has been moved to 5.16

[reviewer notes-]

5.12 Does participation in this research study offer the potential for direct benefit to the research subjects?

Yes - Describe the direct benefit that subjects may receive as a result of study participation. Indicate if all, or only certain, of the subjects may derive this potential benefit.

Describe the benefit:
This study is being performed to advance medical knowledge in general and is not specifically intended to diagnose any illness that an individual may have. However, all participants will benefit by obtaining appropriate calcium and vitamin D supplementation, which is currently only given to approximately 12 and 5% (respectively) of nursing home residents in the Pittsburgh area. Patients with vitamin D deficiency will be identified and treated prior to study entry. Previous studies have shown that the addition of calcium and vitamin D in nursing home residents reduces hip fractures by 43% and other non-vertebral fractures by 32% (28). Bone mineral content of the hip, spine, forearm, VFA and total body will be assessed for each participant.

5.13 Describe the data and safety monitoring plan associated with this study. If the research study involves multiple sites, the plan must address both a local and central review process.

The PI will monitor data quality, patient safety, recruitment, and retention, and study progress on a weekly basis and report it annually to the IRB at the time of study renewal. Adverse events will be reported to the IRB in compliance with the IRB policy as outlined in Chapter 3 of the IRB Reference Manual. All serious adverse events related to the study will be reported to the IRB within 24 hours.

At each nursing home and assisted living facility, we will enlist the paid support of a staff nurse to help with recruitment, retention, and adverse events. At assisted living facilities, we will not have this same type of close observation to obtain information regarding adverse events. Drs. Greenspan, Nace, and Resnick will work with the staff nurse and director of each assisted living facility to develop a mechanism to obtain adverse events in a timely and accurate manner. This may involve contacting the participants between study visits. Per the recommendation of the DSMB on 9/8/2009, we will assess AEs and SAEs by performing a chart review for participants at the Month 1 and Month 3 time points after infusion.

Advisory Panel: We will convene a group of advisors with expertise in nursing home and osteoporosis research to help facilitate the study. The panel will be separate from the DSMB. Panel members are Stephanie Studenski, MD, MPH (Professor of Medicine, Division of Geriatric Medicine, University of Pittsburgh), Jane A. Cauley, DrPH (Professor of Epidemiology, Graduate School of Public Health, University of Pittsburgh), and Joseph Hanlon, PharmD (Professor of Medicine, Division of Geriatric Medicine, University of Pittsburgh). Following study initiation, they will meet by teleconference every 3-6 months to provide input on overall safety, clinical issues, recruitment and retention of nursing home patients, interaction with nursing home staff, administration, family interactions, data collection, and any other issues regarding the study.

Data and Safety Monitoring Board (DSMB): The PI will work with the NIH/NIA program administrator to select individuals with appropriate expertise for a Data and Safety Monitoring Board (DSMB). The DSMB will meet prior to study initiation to review the protocol, informed consent, manual of procedures, Institutional Review Board and General Clinical Research Center applications, and data collection forms. The DSMB members will meet every 6 months...
Section: Section 5 - Potential Risks and Benefits

by teleconference, and the senior statistician will participate in all sessions. At each meeting, they will review overall recruitment, minority recruitment, retention, compliance, adherence, safety, adverse events, quality control, and data management. They will also review and approve the minutes of the previous meeting. Areas that need additional data analysis or protocol changes will be identified, and recommendations will be made regarding continuation of the study. The minutes and reports generated from these meetings will be submitted to the IRB.

Confidentiality will be maintained by a data coding system. Results obtained from individual subjects will be analyzed, reported, and discussed only in reference to the subject identification code. When data are discussed with subjects on an individual basis, only that subject’s data will be discussed. If volunteers request further information, they will be informed of the general findings and that the conclusions of the study will not be released until after all patients have completed their participation at the end of the study.

5.14 What precautions will be used to ensure subject privacy is respected? (e.g. the research intervention will be conducted in a private room; the collection of sensitive information about subjects is limited to the amount necessary to achieve the aims of the research, so that no unneeded sensitive information is being collected, drapes or other barriers will be used for subjects who are required to disrobe)

All efforts will be made to ensure research subject privacy and study staff are trained to maintain subject privacy. Information solely related to the research study will be collected as outlined in the protocol and consent documents. Tests are done in a private room except for the walking test, which is done in a cleared hallway to protect participant privacy.

5.15 What precautions will be used to maintain the confidentiality of identifiable information? (e.g., paper-based records will be kept in a secure location and only be accessible to personnel involved in the study, computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords, prior to access to any study-related information, personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable information, whenever feasible, identifiers will be removed from study-related information, precautions are in place to ensure the data is secure by using passwords and encryption, because the research involves web-based surveys, audio and/or video recordings of subjects will be transcribed and then destroyed to eliminate audible identification of subjects)

All research staff have been trained in matters of subject confidentiality and have completed education modules on various aspects of human research subject protection including confidentiality. Confidentiality will be maintained by a data coding system. Results obtained from individual subjects will be analyzed, reported, and discussed only in reference to the subject identification code. When data are discussed with subjects on an individual basis, only that subject’s data will be discussed. If volunteers request further information, they will be informed of the general findings and that the conclusions of the study will not be released until after all patients have completed their participation at the end of the study. Paper-based records are kept in a secure location at the Osteoporosis Prevention and Treatment Center and are only accessible to research staff involved in the study. Computer-based files are available only to research staff involved in the study and are protected through access privileges and passwords.

5.16 If the subject withdraws from the study, describe what, if anything, will happen to the subject's research data or biological specimens.

If a subject decides to withdraw from study participation, any identifiable medical record information recorded for, or resulting from, their participation in this research study prior to
5.17 Following the required data retention period, describe the procedures utilized to protect subject confidentiality. (e.g., destruction of research records; removal of identifiers; destruction of linkage code information; secured long-term retention)

Following the required data retention period for this study of a minimum of 7 years by University of Pittsburgh policy, the research records will be stored in secured long-term retention.
6.1 Will research subjects or their insurance providers be charged for any of the procedures (e.g., screening procedures, research procedures, follow-up procedures) performed for the purpose of this research study?
* No

6.2 Will subjects be compensated in any way for their participation in this research study?
* yes

6.2.1 Describe the amount of payment or other remuneration offered for complete participation in this research study.
Participants will receive a $10 gift certificate for each completed visit, for a total of 7 visits ($70 total in gift certificates if all 7 visits are completed). Participants who qualify for the study will also receive a ZEST study sweatshirt and sweatpants. Participants in the high resolution wrist MRI substudy will receive a $25 gift certificate for each completed substudy visit, for a total of 2 visits ($50 total in gift certificates if both substudy visits are completed). Participants who continue in the 1-year extension phase will receive a $10 gift certificate at the completion of the Month 36 ($10 total in gift certificates for the extension phase).

6.2.2 Describe the amount and term of payment or other remuneration that will be provided for partial completion of this research study.
Payment is made at the conclusion of each study visit and not as one final payment at the end of the study in the amounts stated in section 6.2.1 ($10 gift certificate for each completed study visit and $25 for each completed substudy visit).
7.1 Summarize the qualifications and expertise of the principal investigator and listed co-investigators to perform the procedures outlined in this research study.

Susan L. Greenspan, MD, Principal Investigator:
Dr. Susan Greenspan is well-qualified to direct the present proposal. She is board-certified in internal medicine, geriatrics, and endocrinology and metabolism, and currently holds joint appointments in the Division of Endocrinology and Metabolism and the Geriatrics Division of the University of Pittsburgh Medical Center (UPMC). Dr. Greenspan is Professor of Medicine at University of Pittsburgh School of Medicine and is based in the Division of Endocrinology and Metabolism at UPMC, where she is Director of the Osteoporosis Prevention and Treatment Center. She is also Associate Program Director of UPMC’s General Clinical Research Center located in Montefiore University Hospital.
From 1990 to 1999, Dr. Greenspan directed the Osteoporosis Prevention and Treatment Center and Bone Density Testing Center at Beth Israel Deaconess Medical Center (BIDMC) in Boston. In 1996, she was appointed Associate Program Director of the Harvard-Thorndike General Clinical Research Center at BIDMC. She was promoted to Program Director in December 1998, and was responsible for all clinical research conducted in the General Clinical Research Center (150 investigators, 65 active protocols) until her relocation to Pittsburgh in September 1999.
Over the past 15 years, Dr. Greenspan has published numerous papers on bone and mineral metabolism topics, including maintenance of skeletal integrity in elderly men and women, assessments of new techniques and devices for classification of bone status, new biochemical markers of bone turnover for therapeutic assessment, and risk factors for falls and fractures in elderly men and women. She is currently involved in ongoing clinical trials at UPMC and at BIDMC in Boston, where her NIH R01 is being completed.

Mary Anne Ferchak, RN, BSN:
Mary Anne Ferchak is a registered nurse with the Osteoporosis Prevention and Treatment Center at the University of Pittsburgh and will be one of two coordinators for this study.

Julie Wagner, PA-C, MPA, Co-Investigator:
Julie Wagner is a certified physician assistant with the Osteoporosis Prevention and Treatment Center at University of Pittsburgh. She currently is a co-investigator in other clinical research studies with Dr. Susan Greenspan and will provide clinical support for this study.

Karen Vujevich, CRNP, Co-Investigator:
Karen Vujevich is a family health certified registered nurse practitioner with the Osteoporosis Prevention and Treatment Center at University of Pittsburgh. She is currently coordinates other clinical research studies for Dr. Greenspan and will provide clinical support.

Megan Miller, BS, CCRC, Co-Investigator:
Megan Miller has a BS degree in biology, is a clinical research coordinator with the Osteoporosis Prevention and Treatment Center at the University of Pittsburgh, and is certified in phlebotomy through UPMC and certified as a clinical research coordinator through the Association of Clinical Research Professionals (ACRP). She currently coordinates other clinical research studies with Dr. Susan Greenspan.

Pouran Famili, DMD:
Dr. Famili is currently a Professor of dental medicine at the University of Pittsburgh School of Dental Medicine and Chair of the Department of Periodontics and is a co-investigator on this study. She will be performing the dental exams and supervising residents from the periodontal department who may also perform the dental exams.

Neil Resnick, MD:
Dr. Resnick is the Chief of the Division of Geriatric Medicine at the University of Pittsburgh Medical Center and oversees all clinical activity in UPMC-affiliated nursing homes. He is also
Section: Section 7 - Qualifications and Source(s) of Support

the Director of the University of Pittsburgh Institute on Aging, which is designed to improve the quality of healthcare for older adults throughout the greater Pittsburgh region. He has collaborated with the PI on multiple geriatric studies, and is a co-investigator on this protocol.

David Nace, MD;
Dr. David Nace is the Director of Long Term Care at the University of Pittsburgh and has a solid track record in clinical research, program development, education, and quality of life in the long term care setting. He is a co-investigator on this study.

Rollin Wright, MD;
Dr. Wright is board certified in internal medicine, and she has a certificate of added qualifications in geriatrics. She is an assistant professor in the Division of Geriatric Medicine at the University of Pittsburgh Medical Center (UPMC) and has collaborated with the PI on other research studies. Dr. Wright will be a co-investigator on this study.

Roberta M. Churilla, CRNP, MSN
Roberta Churilla is a nurse in the Division of Geriatric Medicine who has coordinated other research studies and will help with various aspects of this study.

Carroll Lee, RN, BSN
Carroll Lee is a nurse with the Osteoporosis Prevention and Treatment Center who will be one of the coordinators for this study.

Abbe de Vallejo, PhD.
Dr. de Vallejo is tenured Associate Professor of Pediatrics and Immunology, and faculty member of the Pittsburgh Cancer Institute, the McGowan Institute of Regenerative Medicine, and the Children's Hospital of Pittsburgh. He is a co-investigator on this study.

Gail Fiorito, BA, RT(R)
Gail Fiorito has a BA from La Roche College and an AS from Penn State. She is a board certified x-ray technologist and certified DXA technologist.

7.2 Indicate all sources of support for this research study.

* Selections

Federal: Upload a copy of the entire grant application (including the cover sheet) if our site is the awardee institution; for federal contracts, upload a copy of the research plan.

Industry - Includes monetary support and/or provision of drugs or devices

If Federal support, provide the sponsor information:

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For projects not supported by a federal grant, upload the research plan that was submitted for funding:
Name Modified Date
7.3 **Is this study funded in part or whole by a PHS Agency?** (click here for list of PHS Agencies)
### Other Attachments (e.g., Reference List)

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### Appendix 1: Procedures and Locations

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<td>M12</td>
<td>M24</td>
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<td>Food Frequency Calcium Questionnaire</td>
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<td>Depression Questionnaire (PHQ-9)</td>
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<td>High Resolution Wrist MRI Substudy</td>
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<td>microMRI scan**</td>
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* **Note:** The table includes various procedures and assessments related to medical care, including screenings, laboratory tests, and diagnostic procedures. The entries indicate the frequency and timing of these procedures across different care facilities and study stages. The asterisks and footnotes indicate specific details or exceptions to the general procedure frequency.
No more than 30 ml (approx. 2 tbsp.) will be drawn at each study visit, for a total of approx. 140 ml (approx. 9 tbsp.) for the entire study. Due to the fragile nature of the specimens, which may deteriorate or become damaged while being transported to the CTRC for processing, it may be necessary to perform repeat blood tests. Blood samples may be obtained within a 2 week window to avoid protocol deviations in the event of unsuccessful attempts to draw blood on the day of the study visit due to patient factors such as dehydration.

* The procedures and tests at M12, M24 and M36 may occur over several days in deference to patient schedules and needs. The total time needed to complete the procedures and tests is approx. 3 hours. If assessments for function, depression or cognition are interrupted by patient needs before completion, the test will be repeated from the beginning at the next opportunity for that study visit.

** Two Informed Consent Documents (One for screening procedures, one for study participation). Informed consent may be obtained on a day prior to the screening or study procedures being performed to accommodate schedules of family members.

*** Randomization visit procedures may occur over several days instead of at a single visit

**** An addendum consent will be used for the 1-year extension phase which involves a Month 36 follow-up visit. All subjects randomized into the study are eligible to participate in the 1-year extension phase, and informed consent will be obtained at any point in the study prior to the M36 study visit for subjects wishing to participate.

Dental exams will be performed at the patient’s care facility by Dr. Famili or by resident from periodontics department supervised by Dr. Famili. Screening dental exams will be performed following consent procedures but not necessarily on the same day as the other screening visit tests. Dental exams at M12 and M24 may occur ± 30 days of those study visit dates.

Serum calcium only

Two days after we administer zoledronic acid IV, we will re-evaluate participants’ renal status (estimated GFR, serum creatinine, serum calcium, albumin, hematocrit and hemoglobin will be measured at the participant’s care facility).

BUN, serum calcium, serum creatinine, LFTs, albumin, hematocrit and hemoglobin

Authorization for release of medical records in the event of adverse events or death

Minimum Data Set Form (MDS), information that nursing homes routinely collect on all their patients and is part of the patient’s medical record.

PTH included in screening/safety labs at screening visit only.

Screening 25 OH vili D may be repeated if participant needs vitamin D repletion.

DXA is the final stage of the screening process and will be performed prior to the randomization procedures. Only eligible subjects will be randomized and undergo the randomization procedures.

For a subset of 60 subjects (30 randomized to zoledronic acid, 30 randomized to placebo), Subjects will be consented for the substudy using a separate consent form prior to being transported to the UPMC MR Research Center.

History at screening only; Brief physical exam with vital signs at follow-up visits. Height and weight at screening, M6, M12, and M24.

Long-term follow-up for fracture queries will occur approximately every 6 months following the M24 study visit until all participants have completed 24 months of long-term follow-up (via telephone contact for subjects able to self-report and via medical record review for subjects not able to self-report). Information collected from medical records for long-term follow-up will be limited to information related to bone health, fractures and mortality.

BUN, serum calcium, serum creatinine, alkaline phosphatase, albumin, and estimated GFR at M36 for participants enrolled in the 1-year extension