University of Pittsburgh
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STUDY PROTOCOL WITH STATISTICAL ANALYSIS PLAN

Official Title: The Impact of Osteoporosis Medications on Muscle Health in Older Adults

Short Title: MITO (Muscle Impact of Treating Osteoporosis)

ClinicalTrials.gov Identifier: NCT05666310

Other Study ID Number: University of Pittsburgh IRB: STUDY22080139

Document Date: Effective September 19, 2023 (IRB-approved protocol, STUDY22080139)

Note: This document is the complete IRB-approved study protocol, including study objectives, design, methods, eligibility, endpoints, and the statistical analysis plan. All amendments approved by the University of Pittsburgh IRB prior to submission are incorporated.

University of Pittsburgh | PittPRO

Date: Wednesday, August 26, 2026 3:21:31 PM Print Close

STUDY22080139 Basic Study Information

Basic Study Information

1. * Title of study:
   The Impact of Osteoporosis Medications on Muscle Health in Older Adults

2. * Short title:
   MITO (Muscle Impact of Treating Osteoporosis)

3. * Brief description:
   Osteosarcopenia is a geriatric musculoskeletal syndrome characterized by co-existence of osteoporosis and sarcopenia (low skeletal muscle mass, strength, and/or functional capacity). This condition is associated with reduced physical performance including activities of daily living, falls and fractures, and ultimately increased mortality. There is strong evidence of overlap between the pathophysiology of osteoporosis and sarcopenia. To date, most of the pharmacotherapies for osteosarcopenia target predominantly osteoporosis, and information about their impact on muscle health is limited. This research plan will further explore the relationship between bone and muscle, and provide new information about effect of osteoporosis medications (denosumab and zoledronic

acid on muscle health in older adults who are under treatment for osteoporosis. We will accomplish this goal through the following specific aims: 1) Evaluate the impact of two different classes of osteoporosis medications on longitudinal changes in skeletal muscle function, strength and lean mass in older adults and; 2) Explore associations between measures of bone mass and skeletal muscle health.

Currently, dual X-ray absorptiometry (DXA) is the most widely use method to examine lean mass. However, DXA is a controversial measure for characterizing sarcopenia and is not well-correlated with muscle strength or function. The deuterated creatine (D3-creatine) dilution method is a novel assessment of total body muscle mass based on the knowledge that nearly all creatine is stored in skeletal muscle, creatine is converted to creatinine at a steady rate, and creatinine is excreted in urine. Zhu and colleagues recently examined this method in a subset of community-dwelling older women in Buffalo, New York who participated in the Women's Health Initiative. They reported moderate correlations with DXA lean mass but those with the highest D3Cr muscle mass had the greatest physical function. Muscle ultrasound is also an inexpensive, feasible and innovative tool to examine muscle mass. Portable ultrasound imaging of the quadriceps muscles can provide information about muscle mass by measuring its cross- sectional area, and thickness without the risk of exposing patients to excess radiation. Multiple studies have confirmed ultrasound is a reliable and valid tool for the assessment of muscle size in older adults. In this study we are planning to use novel methods of assessing lean mass including the D3Cr method and the muscle ultrasound.

4. * **What kind of study is this?**

Single-site study

5. * **Will an external IRB act as the IRB of record for this study?**

○ Yes ● No

6. * Local principal investigator:

Nami Safai Haeri

* Is this your first submission, as PI, to the Pitt IRB?

○ Yes ● No

7. * Does the local principal investigator have a financial interest related to this research?

○ Yes ● No

8. Attach the protocol:

- Sponsor/Multicenter/Investigator-initiated protocol
- Coordinating Center supplement
- Emergency Use Consent/ Protocol/ FDA Form 3926
- Exempt Application form

Document	Category	Date Modified	Document History

There are no items to display

STUDY22080139

Funding Sources

1. * Indicate all sources of support:

External funding

2. * Identify each organization supplying funding for the study:

Funding Source	Sponsor's Funding ID	Grants Office ID	Attachments	Pitt Awardee	Grant Recipient
National Institute on Aging	5P30AG024827			yes	Susan Greenspan, MD Nami Safai Haeri, MD

STUDY22080139 Local Study Team Members

Study Team Members

1. * Identify each person involved in the design, conduct, or reporting of the research:

Name	Roles	Department/School	Affiliation	Involved in Consent	Qualifications	Financial Interest
Janelle Christensen	Key Personnel / Support Staff	U of Pgh | School of Medicine | Medicine	Pitt staff	yes	Janelle Christensen PhD, is a research coordinator with the Division of Geriatric Medicine at the University of Pittsburgh.	no
Carly Estocin	Key Personnel / Support Staff	U of Pgh | School of Medicine | Medicine	Pitt staff	yes	Carly Estocin, BSN, has experience in internal medicine and oncology, specifically in stem cell transplantation and Car T-cell infusion as well as re... view all	no

Name	Roles	Department/School	Affiliation	Involved in Consent	Qualifications	Financial Interest
Nicholas Gatto	Key Personnel / Support Staff	U of Pgh | Dietrich School of Arts and Sciences | Biological Sciences	Pitt staff	no	Nicholas Gatto is the regulatory and IRB coordinator in the division of geriatric medicine.	no
Susan Greenspan	Co-investigator Faculty Mentor	U of Pgh | School of Medicine | Medicine	Pitt faculty	yes	Dr. Susan Greenspan, MD is PI and also faculty mentor for this project. She is also the research director of Pittsburgh Pepper center.	no
Bari Guzikowski	Key Personnel / Support Staff	Other	Pitt staff	yes	Bari Guzikowski is the administrative assistant to Dr. Greenspan with the Osteoporosis Prevention and Treatment Center at the University of	no

Name	Roles	Department/School	Affiliation	Involved in Consent	Qualifications	Financial Interest
					Pittsburg... view all	
Kelley KOrff	Key Personnel / Support Staff	Other	Pitt staff	yes	Kelley Korff, RN is going to mainly assist with administration of study medications. She has been part of Dr. Greenspan's group for many years and ha... view all	no
Elena Loedding	Key Personnel / Support Staff Administrator	U of Pgh | School of Medicine | Medicine	Pitt staff	no	Elena Loedding is the administrative assistant to Dr. Greenspan with the Osteoporosis Prevention and Treatment Center at the University of Pittsburg.... view all	no
KPG Subashan	Statistician	U of Pgh | School of Medicine |	Pitt faculty	no	Dr. Subashan Perera PhD	no

Name	Roles	Department/School	Affiliation	Involved in Consent	Qualifications	Financial Interest
Perera		Medicine			has collaborated with the co-PI over the past 10 years and is the lead biostatistician for the NIH-funded Pepper grant.	
Nami Safai Haeri	Principal Investigator	U of Pgh | School of Medicine | Medicine	Pitt faculty	yes	Dr. Nami Safai Haeri, MD is currently a Pepper scholar and faculty member in division of geriatric medicine and PI of this study.	no

2. External team member information: (Address all study team members in item 1. above and leave this section blank)

Name	Description
There are no items to display	

3. Have you, Nami Safai Haeri, verified that all members of the research team have the appropriate expertise, credentials, training, and if applicable, child clearances and/or hospital privileges to perform those research procedures that are their responsibility as outlined in the IRB

application?

* ● Yes ○ No

Study Scope

Check all that apply

1. * Will this study actively recruit any of the following populations?

- [ ] Adults with impaired decision-making capacity
- [ ] Children (under the applicable law of the jurisdiction in which the research will be conducted (<18 years for PA))
- [ ] Children who are Wards of the State
- [ ] Employees of the University of Pittsburgh/UPMC
- [ ] Medical Students of University of Pittsburgh as primary research group
- [ ] Nursing School Students of University of Pittsburgh as primary research group
- [ ] Students of the University of Pittsburgh
- [ ] Neonates of uncertain viability
- [ ] Non-viable neonates
- [ ] Non-English speakers
- [ ] Nursing home patients in the state of Pennsylvania
- [ ] Pregnant women
- [ ] Prisoners
- [x] N/A

2. * Will any Waivers be requested?

- [ ] Waiver/Alteration of Consent
- [x] Waiver to Document Consent
- [x] Waiver/Alteration of HIPAA
- [ ] Exception from consent for emergency research
- [ ] N/A

3. * Will this study involve any of the following?

- [x] Specimens
- [ ] Honest Broker to provide data/specimens
- [x] Return of Results to Subjects or Others
- [ ] Fetal tissue
- [ ] N/A

4. * Will Protected Health Information be collected?

- [ ] Pitt medical records
- [x] UPMC medical records
- [x] Other Institutions' medical records
- [ ] N/A

5. * Other Requests?

- [ ] Deception (if not Exempt, also requires Waiver/Alteration of Consent)
- [ ] Emergency Use / Single Patient Expanded Access (using FDA Form 3926)
- [ ] Placebo Arm
- [ ] Withdraw from usual care
- [x] N/A

6. * Determining Scientific Review:

Received External funding where scientific merit was established as a condition of funding

7. * Has this study (or substantially similar study) been previously disapproved by the Pitt IRB or, to your knowledge, by any other IRB?

○ Yes ● No

Review the HRPO policy, if participating in research at the VA Pittsburgh Healthcare System or using funding from the VA

8. * Does the study use an approved drug or biologic, use an unapproved drug or biologic, or use a food or dietary supplement to prevent, diagnose, cure, treat, or mitigate a disease or condition?

● Yes ○ No

9. * Does the study evaluate the safety or effectiveness of a device (includes in-vitro laboratory assays)?

○ Yes ● No

10. * Is this application being submitted to convert an approved study from OSIRIS to PittPRO? (Tip Sheet)

○ Yes ● No

11. * Does your research protocol involve the evaluation or use of procedures that emit ionizing radiation and, after reviewing this HUSC guidance, does your research protocol require HUSC review? (If yes, upload the HUSC form in the Local Supporting Documents section). If you are unsure of review requirement, select yes.

● Yes ○ No

STUDY22080139 Local Research Locations

Research Sites

1. **Choose all sites that apply:**

   University of Pittsburgh
   UPMC

   *** Select the University of Pittsburgh sites where research will be conducted:**

   Main Campus – Pittsburgh

   List university owned off-campus research sites if applicable:

   Pepper SMART center

   *** Select the UPMC sites where research will be conducted:**

   Other UPMC Site- Specify below:

   List the Other UPMC sites:

   UPMC Benedum Geriatric Clinic

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

   The research team has appropriate resources and adequate facilities available for the conduct of this study. The Pittsburgh Pepper center owns a GE Healthcare NextGen LOGIQ* e R7 Compact Digital Ultrasound Console, a Hologic Discovery Bone Densitometer with fan beam technology and Vertebral Fracture Assessment and Mobility and Research Training (SMART) Center. The University of Pittsburgh Center for Research on Health Care Data Center will perform data management for the study. The PI and research staff are well-trained and experienced in the conduct of research studies, and all study personnel have completed the CITI Modules in Research Integrity, Human Subject Protection, Conflict of Interest, HIPAA Researchers Privacy requirements, and Good Clinical Practice.

STUDY22080139

Drugs

1. * List all drugs, biologics, foods, and dietary supplements to be used in the study:

	Generic Name	Brand Name	FDA status	Evaluation Increase Risk	Data Reported to FDA	Attachment Name
View	Zoledronic Acid	Reclast	Meets current FDA approved indication and usage labeling			Reclast.pdf
View	D3-Creatine		Unapproved drug or biologic			FDA stable isotopes_Version_0.01.pdf
View	caltrate 600 + D3 softchews and tablets		Meets current FDA approved indication and usage labeling			
View	denosumab	Prolia	Meets current FDA approved indication and usage labeling			Prolia.pdf
View	Acetaminophen	Tylenol	Meets current FDA approved indication			

Generic Name	Brand Name	FDA status and usage labeling	Evaluation Increase Risk	Data Reported to FDA	Attachment Name

2. * Will the study be conducted under an investigational new drug application (IND) and/or require review by the Human Use Subcommittee (HUSC) of the University of Pittsburgh Radiation Safety Committee?

○ Yes ● No

3. Attach files: (Attach information not related to a specific drug or not already uploaded elsewhere. Attachments may include justification for why an IND is not required, FDA's IND Acknowledgement Letter, or confirmation receipt from submission to FDA.)

Document	Category	Date Modified	Document History
There are no items to display			

4. * Describe your plan to store, handle, and administer drugs so that they will be used only on subjects and be used only by authorized investigators:

The independent research pharmacist at the institutional Investigational Drug Service pharmacy will package drugs/placebos to be similar in appearance; however, the research nurse/PA will be able to tell a difference with the syringes and therefore a dedicated un-blinded research nurse/PA will administer the study drug/placebo injections to maintain the blinding for the rest of the research team. UPMC Investigational Drug Services will store and dispense study drugs and/or placebo as needed to the research staff.

Study statistician will create schedules which link the randomization sequence number, participant identifier and treatment arm, and study team will call in all prescriptions thereafter by the randomization sequence number. We have successfully employed the same process in other ongoing trials.

5. * Do you plan to utilize the UPMC Investigational Drug Service (IDS) to dispense the drug?

● Yes ○ No

STUDY22080139

Local Site Documents

Click **Continue** as this page was intentionally left blank.

STUDY22080139 Recruitment Methods

Recruitment Methods

*** Will you be recruiting individuals for participation in this study?**

● Yes ○ No

1. * Describe who will be recruiting individuals for participation for this study:

Nami Safai Haeri
Susan Greenspan
Janelle Christensen

2. * Select all methods to be used for recruitment:

Directly approaching potential subjects (in-person)
Email/Listserv/Electronic Mailing List
Flyers/Posters or Brochures
Pitt+Me
Registries

* Enter the name of the Registry and IRB number:

Pittsburgh Pepper Older Americans Independence Center Research Registry Database, Pitt Plus Me (Pitt + Me)

3. * Provide details on your recruitment methods:

Subjects will be recruited from community-dwelling oldrer adults who are receiving/are going to start receiving their osteoporosis at the osteoporosis clinic. The will be eligible for treatment of osteoporosis with either Prolia or Reclast based on physicians assessment.

Recruitment will be through direct contacting patients. Research staff will be

available to talk about osteoporosis and muscle health and answer questions.

Patients who are scheduled for an appointment with a study investigator for osteoporosis treatment will be screened for eligibility by their care provider. If eligible for treatment of their osteoporosis with Prolia or Reclast, the investigator will present the study to the patient and if interested, will introduce the patient to the study team or will provide them with contact information.

We are also going to contact (via email or phone call) older adults on Pittsburgh Pepper Older Americans Independence Center and Pitt+Me research registries dataset who have expressed interest to participate in research studies.

4. * **Describe all compensation/incentives offered to participants and timing of these offers:**

To facilitate subject retention and maintain interest in the study, participants who are randomized will receive a small gift such as a study lap blanket, reusable bag, or flashlight as a thank you gift following completion of the study.

We will provide parking vouchers for the baseline, month 6 and month 12 visits.

5. **Recruitment materials:** (attach all material to be seen or heard by subjects, including advertisements and scripts)

	Document	Category	Date Modified	Document History
View	Email Template_Version_0.01.docx(0.01)	Recruitment Materials	5/9/2023	History
View	MITO Flyer .doc(0.01)	Recruitment Materials	1/4/2023	History

STUDY22080139

Study Aims

1. * **Describe the purpose, specific aims, or objectives and state the hypotheses to be tested:**

Since we know most individuals with osteoporosis (low bone density) may also suffer from sarcopenia (low muscle mass, strength/function), our goal is to demonstrate if approved medications for osteoporosis have positive impact on muscle health or not.

We propose to conduct a 1-year, randomized, double-blind, calcium-vitamin D controlled trial to test the efficacy and predictability of the antiresorptive RANK ligand inhibitor, denosumab, and osteoclast inhibitor (zoledronic acid) on muscle health of a cohort of 40 women ≥65 years old with osteoporosis.

Our hypothesis is Older adults on denosumab (a RANKL inhibitor) will exhibit greater preservation or improvement in lean mass, grip strength and muscle function (Short Physical Performance Battery) over 12 months compared to placebo while those on zoledronic acid (an osteoclast inhibitor) or no treatment will not. We propose the following specific aims:

1) Evaluate the impact of two different classes of osteoporosis medications on longitudinal changes in skeletal muscle function, strength and lean mass in older adults and;
2) Explore associations between measures of bone mass and skeletal muscle health.

2. * **Describe the relevant prior experience and gaps in current knowledge including preliminary data. Provide for the scientific or scholarly background for, rationale for, and significance of the research based on existing literature and how it will add to existing knowledge:**

Sarcopenia is a geriatric syndrome which indicates progressive and generalized loss of skeletal muscle. This condition is associated with reduced physical performance including activities of daily living, falls and fractures, and ultimately increased mortality.

The assessment of muscle mass in frail older adults is important as we try to characterize sarcopenia and improve muscle mass, strength, and function. Although we can measure lean mass by dual X-ray absorptiometry (DXA), DXA is a controversial measure for characterizing sarcopenia and is not well-correlated with strength or function.

The deuterated creatine (D3-creatine) dilution method is a novel assessment of total body muscle mass based on the knowledge that nearly all creatine is stored in skeletal muscle, creatine is converted to creatinine at a steady rate, and creatinine is excreted in urine. Zhu and colleagues recently examined this method in a subset of community-dwelling older women in Buffalo, New York who participated in the Women's Health Initiative. They reported moderate correlations with DXA lean mass but those with the highest D3Cr muscle mass had the greatest physical function. However, this method has never been used to assess muscle mass changes following treatment with osteoporosis medications including Reclast and Prolia.

Muscle ultrasound is also an inexpensive, feasible and innovative tool to examine muscle mass. Portable ultrasound imaging of the quadriceps muscles can provide information about muscle mass by measuring its cross- sectional area, and thickness without the risk of exposing patients to excess radiation. Multiple studies describing the validity of ultrasound to predict lean body mass showed good validity as compared with DXA ($r^2 = 0.92$ to 0.96) and confirmed ultrasound is a reliable and valid tool for the assessment of muscle size in older adults. To the best of our knowledge, this method has never been used to assess muscle mass changes following treatment with osteoporosis medications including Reclast and Prolia.

Study Design

1. **Total number of subjects to be enrolled at this site (enter -1 for chart reviews, banking, registries):**
   22

2. **Describe and explain the study design:**
   Prospective, interventional randomized (double blind doubly dummy) trial of DXA scan, D3-creatine testing, and muscle ultrasound for examining associations between bone health and muscle mass and muscle function parameters in older adults.

   As this is a preliminary pilot study with a limited sample size, we will use appropriate descriptive statistics, magnitudes of model estimates and graphical methods using data at the individual level (such as spaghetti plots) in addition to standard analytic techniques to draw conclusions. Such graphical techniques focused on individual-level data have been used in other small studies from a range of disciplines. For the Aim 1 standard analyses, we fill first compare the baseline characteristics of the two groups of participants using independent samples t-, Wilcoxon rank sum, chi-square and Fisher's exact tests. Any significant differences will be noted and controlled for as covariates in adjusted analyses. Next, to examine between group differences, we will fit a series of analysis of covariance (ANCOVA) models with each of the baseline to 12-month change in outcomes as the dependent variable; participant group (zoledronic acid/denosumab) as the main independent factor if interest; baseline value of outcome as a covariate; and any other characteristics found to be significantly different at baseline as additional covariates. We will limit the total number of independent variables to a maximum of 6 in view of the limited sample size and the desire to have at least 10 observations per variable. Magnitude and statistical significance of the participant group coefficient will serve as preliminary

evidence supporting the Aim 1 hypothesis. For Aim 2 cross-sectional associations, we will compute Pearson product moment and Spearman rank correlation coefficients between measures of bone and muscle health at baseline. Longitudinal correlations will be computed between 12-month changes in measures of bone and muscle health with and without stratification by participant group. We will also consider partial correlation coefficients for examining longitudinal associations controlling for baseline values and other covariates deemed important.

3. Describe the primary and secondary study endpoints:

DXA Bone mineral density (BMD), DXA Trabecular bone score (TBS), Muscle mass measured by D3-creatine (%), DXA of lean mass (kg), grip strength (kg), gait speed (m/s), rectus femoris muscle thickness and cross-sectional surface area and muscle functional status once at baseline and once 12 months.

4. Provide a description of the following study timelines:

Duration of an individual subject's active participation:

12 months

Duration anticipated to enroll all subjects:

12 months

5. List the inclusion criteria:

Ambulatory adults age ≥65 years including those using assistive devices to maximize generalizability, if they have criteria for treating osteoporosis including: a) osteoporosis by axial bone density (spine, hip or forearm BMD T-score ≤-2.5 SD) or b) a previous adult fragility fracture of the spine or hip; or, c) would be treated based on FRAX National Osteoporosis Foundation treatment thresholds of a 10-year risk of ≥ 20% for a major osteoporotic fracture or ≥ 3% for hip fracture using femoral neck BMD. (these are criteria set by the National Osteoporosis Foundation as eligibility criteria for osteoporosis treatment).

6. List the exclusion criteria:

Patients with a calculated creatinine clearance < 35 ml/min (since zoledronic acid is contraindicated in creatinine clearance < 35) or who have a contraindication for bisphosphonates and denosumab.

Those who are scheduled for a tooth extraction to avoid jaw osteonecrosis. (since osteonecrosis of jaw is a very rare side effect of zoledronic acid and denosumab)

Subjects with severe liver disease. (as these treatments are not appropriate in advanced liver disease)

Those who have been on oral bisphosphonates for the past 1 year and iv bisphosphonates for the past 2 years prior to the study (as effect of these medications will last 1-2 years and prior consumption may affect the result)

Men (since osteoporosis is more common in women)

7. Will children or any gender, racial or ethnic subgroups be explicitly excluded from participation?

● Yes ○ No

* Identify the subgroups and provide a justification:

Men, because they do not become postmenopausal and are less likely to become osteoporotic and osteoporosis.

Children because study is in older adults.

8. Describe the power analysis used and cite your method of statistical analysis. If a power analysis is not possible, thoroughly justify the sample size required for the study, including appropriate literature citation (alternatively provide page reference in attached protocol):

This is an initial small pilot study, and unlike larger definitive studies, sample size and

power computations strictly based on rejection of null hypotheses at the 0.05 level are not appropriate. Findings from the proposed study will be used for rigorous sample size and power computations in planning larger studies that use the same novel outcomes. The sample size of 11 per group is also consistent with the generally accepted range for a group in other pilot studies from a range of disciplines in health sciences (refs).

Refs.

Duncan P, Richards L, Wallace D, Stoker-Yates J, Pohl P, Luchies C, Ogle A, Studenski S. A randomized, controlled pilot study of a home-based exercise program for individuals with mild and moderate stroke. Stroke. 1998 Oct;29(10):2055-60. doi: 10.1161/01.str.29.10.2055. PMID: 9756581.

VanSwearingen JM, Perera S, Brach JS, Cham R, Rosano C, Studenski SA. A randomized trial of two forms of therapeutic activity to improve walking: effect on the energy cost of walking. Journals of Gerontology-Medical Science 2009 Nov; 64A(11): 1190-1198. PMCID: PMC2981453

Weiner DK, Gentili A, Rossi M, Coffey-Vega K, Rodriguez KL, Hruska KL, Hausmann L, Perera S. Aging Back Clinics - a geriatric syndrome approach to treating chronic low back pain in older adults: results of a preliminary randomized controlled trial. Pain Medicine 2020 Feb; 21(2): 274-290. doi: 10.1093/pm/pnz179

STUDY22080139

Research Activities

1. * **Provide a detailed description of all research activities (including screening and follow-up procedures) 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.**

Subjects will have 4 visits:

1. Informed consent and then screening (review of medical records and participants medical history/questionnaires)
2. Baseline (DXA, collection of urine for D3-Creatine, muscle Ultrasound, SPPB, gait speed, grip strength) and M0 denosumab or zoledronic acid administration (with the placebo of the other drug)
3. M6 denosumab or placebo administration
4. 12-month assessment (DXA, collection of urine for D3-Creatine, muscle Ultrasound, SPPB, gait speed, grip strength) and M12 Reclast administration to everyone

All of the below procedures will be performed at the Osteoporosis Prevention and Treatment Center (Kauffman building in Oakland, Pittsburgh)

D3-Creatine: An oral dose of 30 mg D3-creatine (D3Cr; Cambridge Isotope Laboratories, Inc., Tewksbury, MA) supplied by Dr. William Evans (consultant) will be mailed to patient. They will ingest the capsule 2-4 days prior to the baseline and 12 months visit where they will provide an 8h fasting spot urine sample. We will do brief SPPB and physical exam at their baseline visit procedures, and month 12 procedures. Urine samples will be stored at -20°C, de-identified and shipped to Dr. William Evans's lab (consultant) at the University of California, Berkeley for analysis. D3-creatine and unlabeled creatinine will be measured by liquid chromatography

and tandem mass spectroscopy and then samples will be destroyed. Total body muscle mass will be calculated using established algorithms based on the ratio of labeled to unlabeled urinary creatinine. Archived samples will be labeled with unique codes and will be stored for an indefinite period of time in locked freezers belonging to the University of Pittsburgh Osteoporosis Prevention and Treatment Center. These freezers are under supervision of Dr. Greenspan and are located at the Montefiore Hospital and are monitored by a security alarm service. There are three -20°C freezers, and two -80°C freezers for sample storage, and a -80°C freezer reserved for emergency use. The freezers are monitored 24 hours per day 7 days per week via modem by an outside security company. Urine specimen not sent to Dr. Evans will be stored and used in the future by investigators with approved protocols. These samples will be labeled with a unique code to de-identify them. Future testing may include research on aging, function, bone and muscle health, inflammation, immune response measures, and overall health. Both the creatinine supplement and isotope which make up D3Cr were evaluated for FDA regulatory implications. The clinical investigation is intended only to evaluate the dietary supplement's effect on the structure or function of the body, therefore an IND is not required. Although the creatine will be deuterated, deuterium is a stable isotope and the FDA has developed a policy that if a substance would not otherwise require submission of an IND, then that substance enriched with a stable isotope will not require an IND.

DXA: Total body lean mass (kg) and appendicular lean mass (kg), bone mineral density (BMD) and trabecular bone score (TBS) are obtained from whole body DXA images (Hologic APEX 5.5 software, Bedford, MA). This DXA unit is located at osteoporosis prevention and management center in Oakland. DXA will be performed on M0 and M12 by a UPMC DXA radiology technologist.

Muscle Ultrasound: We will us muscle ultrasound imaging to measure bilateral rectus femoris muscle cross-sectional area, and muscle thickness at baseline and 12 months. This will be performed by the PI. All data collection will be done at osteoporosis prevention and management center in Oakland. We will use portable

B-mode ultrasound (NextGen LOGIQ* e R7, GE Healthcare, Chicago, IL) to image the rectus femoris, one of the four quadriceps muscles.

Physical Function Measures: Physical function measures are currently assessed in the ongoing parent trial. The Short Physical Performance Battery (SPPB) is a well-validated measure of physical function that evaluates balance, time to complete five consecutive chair rises without support, and usual gait speed. Self-report measures including medical history, medication history, history for falls, fractures, will also be collected. Functional measures will be assessed on M0 and M12 by RNs or the PI. As individuals who use assistive devices can be included in the study, please confirm that SPPB and gait speed will still be measured in this group.

Grip Strength: Grip strength (kg) is assessed with a hand-held dynamometer (Jamar Plus Digital Hand Dynamometer, Sammons Preston, Bolingbrook, IL). Participants are seated with their elbow flexed at 90 degrees. Participants perform one test trial, followed by three alternative trials for each hand with rest periods between trials. The best measurement is used for analyses. Grip strength will be measured on M0 and M12 by RNs or the PI.

Gait Speed: Participants begin from a standing position and walk at their self-selected speed over a 4-meter course while a research coordinator measures the time using a stopwatch. Participants are allowed use of their assistive device if it is their customary mode of walking. Two trials are performed, and the average will be used for data analysis. Gait speed will be measured on M0 and M12 by RNs or the PI.

Study Drug: Every subject will receive an injection (drug or placebo) and IV infusion (drug or placebo) at the baseline visit. Every subject will receive IV zoledronic acid infusion at the M12 visit. Semi-annual denosumab 60 mg subcutaneous injection or placebo injections will be ordered by the study PI and administered by the research nurse or physician's assistant at M0 and M6. Annual zoledronic acid infusions or placebo injections will be ordered by the study PI and administered by the research nurse or physician's assistant at M0, M12.

Calcium and vitamin D supplements are provided by RNs or the PI at the baseline visit. Participants will be recommended to receive a total of approximately 1200 mg calcium daily (dietary plus supplement) and 800-1000 IU daily of vitamin D (dietary plus supplement).

Acetaminophen: will be administered by the RN, 1 hour before the IV infusion and then every 8 hours for the next 72 hours to manage possible flu-like symptoms such as fever. (Acetaminophen will only be given to subjects no more than three times a day, and will only be given as needed).

Randomization and Masking. We will use the high quality pseudo-random deviate generator in SAS® (SAS Institute, Inc., Cary, North Carolina) known to be free of serial correlations to randomize women to the two treatment groups in a 1:1 ratio. Those non-ambulatory will be excluded. We will use a blocked randomization scheme to force a within-stratum balance between the numbers of women in each arm at any point during the recruitment period, and employ a random block size chosen from small even numbers to prevent research personnel from guessing the treatment arm of a would-be participant. Study statistician will create schedules which link the randomization sequence number, participant identifier and treatment arm, and study team will call in all prescriptions thereafter by the randomization sequence number. We have successfully employed the same process in other ongoing trials.

Study Reminders: we will send reminders to study participants regarding their upcoming visit, logistics, D3-creatine intake and urine collection through their Epic medical record application or phone calls.

2. Upload a copy of all materials used to collect data about subjects: (Attach all surveys, interview/focus group scripts, and data collection forms except for case report forms, SCID or KSADS):

	Document	Category	Date Modified	Document History
View	SPPB_Version_0.01.pdf(0.01)	Data Collection	9/19/2022	History
View	SARCf Data collection form PROUD_Version_0.01.pdf(0.01)	Data Collection	9/19/2022	History
View	Physical Performance Test (PPT) (2)_Version_0.01.doc(0.01)	Data Collection	9/19/2022	History
View	Grip Strength with variables (2)_Version_0.01.doc(0.01)	Data Collection	9/19/2022	History
View	Falls Questionnaire (2)_Version_0.01.doc(0.01)	Data Collection	9/19/2022	History
View	Dietary Calcium Questionnaire-2014 (2)_Version_0.01.docx(0.01)	Data Collection	9/19/2022	History

3. * Will blood samples be obtained for research purposes?

○ Yes ● No

Consent Process

IMPORTANT: *If REDCap will be used to obtain consent, contact Health Sciences IT department (hsappsupport@hs.pitt.edu) for assistance in creating a compliant REDCap eConsent framework.*

Enter N/A in response to the following questions if a Waiver of Consent is requested for all research activities or if no subjects are being enrolled.

1. * **Indicate where the consent process will take place and at what point consent will be obtained:**

   When patients see their provider at the Osteoporosis clinic (either in person or virtually), the study will be introduced to them. If they express interest to participate in the study, we are going to further discuss study details and obtain their consent (either in person or virtually through video-visit or over phone). In cases where we discuss the consent virtually, the form will be mailed to patient with a prepaid envelope and patient will sign and send back the consent form.

2. * **Describe the steps that will be taken to minimize coercion and undue influence, including assurance that there is sufficient time for subjects to make an informed decision:**

   Listed physician investigator will obtain consent from all study subjects. Subjects must be cognitively capable of giving informed consent and participating in the 'report back' understanding.

   Participation is voluntary and participants may withdraw their consent for participation at any time. The study coordinator, co-investigators, or research assistants will discuss the nature, purpose, and design of the study with prospective subjects. Potential participants and their families may review the consent forms in advance of meeting with study staff to discuss the study, and the research team and PI are available to answer any questions they may have. Potential participants may

also discuss the study with their personal physicians or other pertinent clinician involved in their care. The PI and research team are also available to family members and authorized legal representatives to discuss the study, consent forms, and answer any questions about the study.

3. **For studies that involve multiple visits, describe the process to ensure ongoing consent:**

To ensure ongoing consent during the study, participants will be asked if they are interested continuing to participate in the study prior to visits and consent will be re-affirmed prior to each ensuing study visit.

4. * **Steps to be taken to ensure the subjects' understanding:**

Informed consent will be obtained from Interested potential participants. Potential risks and benefits will be described orally and in writing. The certification of informed consent statement will be signed by a licensed physician investigator. We will use the teach back method and will also ask them if they have any questions.

5. * **Are you requesting an exception to the IRB policy related to the informed consent process:**

○ Yes ● No

STUDY22080139

Consent Forms

1. Consent Forms:

	Document	Category	Date Modified	Document History
View	ICF(0.10)	Consent Form	8/22/2023	History

Refer to the following templates and instructional documents:

- Guidance - Consent Wording
- Template - Consent Document - Short Form
- HRP-090 - SOP - Informed Consent Process for Research
- HRP-091 - SOP - Written Documentation of Consent

Waiver to Document Informed Consent

This waiver to document informed consent can be requested 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, such as with phone screening).

1. * Identify the specific research procedures and/or the specific subject populations for which you are requesting a waiver of the requirement to obtain a signed consent form:

We request waiver for our study participants for fasting before the consent visit and asking them screening questions and review their medical records.

2. * Select the regulatory criteria applicable to your request:

- ○ 45 CFR 46.117(c)(1) That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern.
- ● 45 CFR 46.117(c)(2) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context
- ○ 45 CFR 46.117(c)(3) If the subjects or legally authorized representatives are members of a distinct cultural group or community in which signing forms is not the norm.

*** Address why the specific research procedures for which you are requesting a waiver of the requirement to obtain a signed consent form presents no more than minimal risk of harm to the research subjects:**

Subjects will be asked to take the D3-creatine capsule 2-4 days prior and fast starting

at 11 PM the night prior to the first study visit. Subjects will then be consented when first arriving for the visit (prior to the start of any other study procedures). The greatest risk of discomfort for fasting is hunger, but we anticipate fasting for ~8-10 hours overnight will be well tolerated. Collection and storage of private health information carries only the risks of breach of confidentiality and personal discomfort with questions, both of which are considered minimal.

*** Justify why the research involves no procedures for which written informed consent is normally required outside of the research context:**

Patients are commonly asked to fast prior to routine laboratory monitoring for clinical care. Consent is not required in this case. D3-creatinine is also a supplement which does not impose any health risks at the quantity used in this capsule. Signed consent is not required for medical history questions. An alteration of HIPAA is requested for the verbal consent to review medical records.

3. * Upload Scripts:

	Document	Category	Date Modified	Document History
View	Waiver to doc_Phone Script_Version_0.01_Version_0.01.docx(0.02)	Waiver Script	5/9/2023	History

STUDY22080139

Waiver/Alteration of HIPAA Authorization

The use or disclosure of PHI involves no more than minimal risk to the privacy of individuals, based on, at least, the presence of the following elements.

1. * **Describe your plan to protect the identifiers from improper use or disclosure:**

   All paper records that could identify participant will be stored in a locked file cabinet, and all electronic records will be stored in password-protected files.

2. * **Describe your plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by the law:**

   We are not collecting any identifiers as part of their medical record review. Those who volunteer for our study (for example through Pitt+Me or other Pepper registry) provide us their name, date of birth, phone and email contact through the registry, thus we do not need to collect these info from their records.

3. * **Describe written assurances that the PHI will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of PHI would be permitted by this subpart:**

   Your medical records will not be reused or disclosed to any other person or entity,

except as required by law, for authorized oversight of the research project, or for other research.

4. * Indicate why the research could not be practicably be conducted without the waiver or alteration:

Many times study participants are not specifically familiar with how osteoporosis is diagnosed or if they have ever been taken a treatment for osteoporosis. For example Raloxifene is a medication that is commonly used for breast cancer, and it is also a treatment for osteoporosis, though it is not commonly recognized by patients as an osteoporosis medication. Those who have history for taking Raloxifene within the past 2 years are not eligible for our study. Or many times they may confuse osteopenia with osteoporosis, thus we need to see their DXA report to confirm the diagnosis. For these reasons we need to have access to their records to assure they are truly eligible for our study.

5. * Indicate why the research could not practicably be conducted without access to and use of the PHI:

The verbal authorization will be requested from subjects who are calling in to indicate their interest and rather then burden this older population with the multiple steps and extra time for obtaining written documents, we want to offer them the convenience of giving their verbal authorization. If subjects prefer to sign a written request, the study team will advise them on the process. If the subject prefers to complete a written request, the study team will assist them with that process.

6. * Explain why the nature and amount of the medical record information to be collected is felt to be the minimum necessary to conduct this research study:

Past medical history (looking for osteoporosis and fracture history), Previous DXA

scan or X-rays to look for formal diagnosis of osteoporosis, Previous use of osteoporosis medications, Labs for kidney function, calcium level.

STUDY22080139

Medical Records

1. You are required to submit this study to the Research Informatics Office, Health Record Research Request (R3). Per UPMC Policy HS-RS0005, all research projects that access or involve UPMC electronic protected health information (e-PHI) must be submitted to R3, with the exception of clinical trials that are contracted through the UPMC Office of Sponsored Programs and Research Support (OSPARS).

   Complete the R3 intake form available at http://rio.pitt.edu/services. An R3

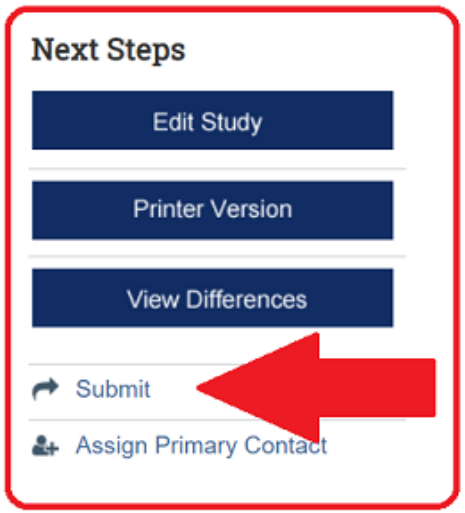
2. [redacted]

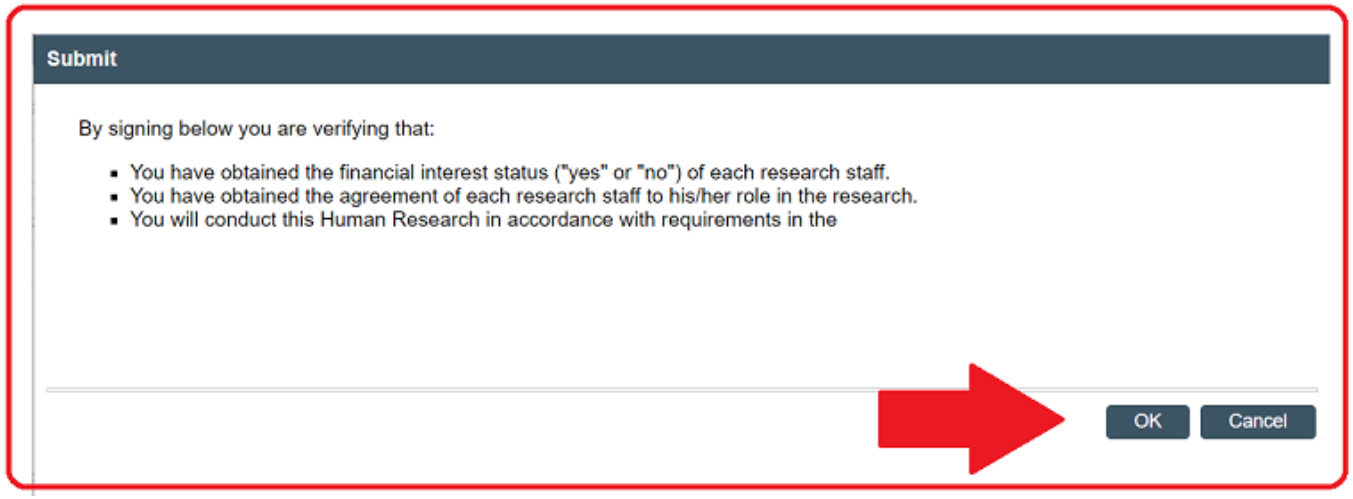









Next Steps
Edit Study
Printer Version
View Differences
Submit
Assign Primary Contact


Submit
By signing below you are verifying that:
You have obtained the financial interest status ("yes" or "no") of each research staff.
You have obtained the agreement of each research staff to his/her role in the research.
You will conduct this Human Research in accordance with requirements in the
OK
Cancel