Document Coversheet

Study Title: Renal Osteodystrophy: A Fresh Approach

Institution/Site:	University of Kentucky
Document (Approval/Update) Date:	ICF 3/13/20; protocol 2/12/20
NCT Number:	NCT02440581
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Coversheet created (AWR):	11/11/22

IRB Approval
2/12/2020
IRB # 43175
IRB6

PROTOCOL TYPE

Which IRB

(•) Medical ( ) NonMedical

Protocol Process Type

( ) Exemption
( ) Expedited (Must be risk level 1)
(•) Full

IMPORTANT NOTE: Once you have saved your choices under "Which IRB" and "Protocol Process Type", you will not be able to change your selections. If you select the wrong IRB Type and/or your application is deemed eligible for a different Protocol Process Type, it may be necessary to create a new application.

Please see below for guidance on which selections to make, and/or go to ORI's "Getting Started" web page. If you still have questions about which IRB or Protocol Process Type to choose, please contact the Office of Research Integrity (ORI) at 859-257-9428 **prior** to saving your selections.

Which IRB

The **Medical IRB** reviews research emanating from the Colleges of Dentistry; Health Sciences; Medicine; Nursing; Pharmacy and Health Sciences; and Public Health.

The **Nonmedical IRB** reviews research originating from the Colleges of Agriculture; Arts & Sciences; Business & Economics; Communications & Information; Design; Education; Engineering; Fine Arts; Law; and Social Work. The Nonmedical IRB does not review studies that involve administration of drugs, testing safety or effectiveness of medical devices, or studies that involve invasive medical procedures, regardless of from what college the application originates.

Which Protocol Process Type

Under federal regulations, an investigator's application to conduct a research project involving human subjects can be processed by the IRBs in three ways:

- by full review;
- by exemption certification;
- by expedited review.

The preliminary determination that a research project is eligible for exemption certification or expedited review is made by the investigator. For assistance in determining which review process type your IRB application is eligible for, please go to ORI's "Getting Started" web page.

The revised Common Rule expanded exemption certification category 4 for certain secondary research with identifiable information or biospecimens. The regulations no longer require the information or biospecimens to be existing. For more information see the Exemption Categories Tool.

PROJECT INFORMATION

Title of Project: (If applicable, use the exact title listed in the grant/contract application).

Renal Osteodystrophy: An Individual Management Approach

Short Title Description

Note: "Short Title" should consist of a couple key words to easily identify your study - these key words (rather than the whole title) will be displayed on the Dashboard in the listing for your study.

Renal Osteodystrophy: An Individual Management App

Anticipated Ending Date of Research Project: 12/31/2021

Number of human subjects 990

Study is/will be open to new subject enrollment or data/specimen collection: (•) Yes ( ) No

PI CONTACT INFORMATION

The Principal Investigator's (PI) contact information is filled in automatically based on who was logged in when the application was created (with LinkBlue ID). If research is being submitted to or supported by an extramural funding agency such as NIH, a private foundation or a pharmaceutical/manufacturing company, the PI listed on the grant application or the drug protocol must be the same person listed below.

If you are not the Principal Investigator, do NOT add yourself as study personnel. You may change the PI contact information on an application that is in Researcher edit mode by:

- clicking the "Change Principal Investigator" link below;
- searching for the PI's name using the search feature;
- clicking "Select" by the name of the Principal Investigator, then "Save Contact Information".

You will automatically be added as study personnel with edit authorization so you can continue editing the application.

Please fill in any blank fields with the appropriate contact information (gray shaded fields are not editable). Required fields left blank will be highlighted in pink after you click "Save".

To change home and work addresses, go to myUK and update using the Employee Self Service (ESS) portal. If name has changed, the individual with the name change will need to submit a 'Name Change Form' to the Human Resources Benefits Office for entering into SAP. The new name will need to be associated with the individual's Link Blue ID in SAP before the change is reflected in E-IRB. Contact the HR Benefits Office for additional information.

Note: Principal Investigator (PI) role for E-IRB access
The PI is the individual holding primary responsibility on the research project with the following permissions on the E-IRB application:

1. Read;
2. write/edit;
3. receive communications; and
4. submit to the IRB (IR, CR, MR, Other Review*).

Change Principal Investigator:

First Name:	Hartmut	Room# & Bldg:	MN564 MED SCIENCE BLDG.
Last Name:	Malluche	Speed Sort#:	405360298
Middle Name	H		
Department:	Internal Medicine - 7H350	Dept Code:	7H350
PI's Employee/Student ID#:	00004116	Rank:	Professor
PI's Telephone #:	8593235049221	Degree:	MD
PI's e-mail address:	hartmut.malluche@uky.edu	PI's FAX Number:	8592571052
PI is R.N.	○ Yes ◉ No	Trained:	Yes
		Date Trained	8/3/2017

Do you, the PI, have a significant financial interest related to your responsibilities at the University of Kentucky (that requires disclosure per the UK administrative regulation 7:2)?

○ Yes ◉ No

RISK LEVEL

Indicate which of the categories listed below accurately describes this protocol

- ○ (Risk Level 1) Not greater than minimal risk
- ◉ (Risk Level 2) Greater than minimal risk, but presenting the prospect of direct benefit to individual subjects
- ○ (Risk Level 3) Greater than minimal risk, no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.
- ○ (Risk Level 4) Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of subjects.

*"Minimal risk" means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves from those ordinarily encountered in daily life or during the performance of routine physical or psychological examination or tests [45 CFR 46.102(i)]

Download UK's guidance document on assessing the research risk for additional information on risk [PDF]

SUBJECT DEMOGRAPHICS

Age level of human subjects: (i.e., 6 mths.; 2yrs., etc..) 21yrs to 90

Indicate the targeted/planned enrollment of the following members of minority groups and their subpopulations
(Please note: The IRB will expect this information to be reported at Continuation Review time):

Enter Numbers Only!

Ethnic Origin	#Male	#Female
American Indian/Alaskan Native:		
Asian:	3	3
Black/African American:	225	225
Hispanic/Latino:	9	9
Native Hawaiian/Pacific Islander:		
White/Caucasian:	267	267
Other or Unknown:		

If unknown, please explain why:

Indicate the categories of subjects and controls to be included in the study. Depending on the subject category applicable to your research you may be required to complete additional forms. [Note, if the study does not involve direct intervention or direct interaction with subjects, (e.g., record-review research, outcomes registries), do not check mark populations which the research does not specifically target. For instance, a large record review of a diverse population may incidentally include a prisoner or an international citizen, but, if the focus or intent of the study has nothing to do with that status, you do not need to check those category(ies).]

Check All That Apply (at least one item must be selected)

- ☐ Children (individuals under age 18)
- ☐ Wards of the State (Children)
- ☐ Emancipated Minors
- ☐ Students
- ☐ College of Medicine Students
- ☐ UK Medical Center Residents or House Officers
- ☐ Impaired Consent Capacity Adults
- ☐ Pregnant Women/Neonates/Fetal

ADDITIONAL INFORMATION:

Please visit the IRB Survival Handbook under the named topic:

- Children/Emancipated Minors
- Students as Subjects
- Prisoners
- Impaired Consent Capacity Adults: Link to required Form

And/Or:

- UKMC Residents or House Officers [see requirement of GME]

Material

- ☐ Prisoners
- ☐ Non-English Speaking
- ☐ International Citizens
- ☐ Normal Volunteers
- ☐ Military Personnel and/or DoD Civilian Employees
- ☑ Patients
- ☐ Appalachian Population

- Non-English Speaking [see instructions for recruitment and E-IRB Research Description section on same topic]
- International Citizens [HTML] (DoD SOP may apply [PDF])
- Military Personnel and/or DoD Civilian Employees (DoD SOP may apply [PDF])

The next questions involve assessment of the study relative to potential recruitment of subjects with impaired consent capacity (or likelihood).

☐ Check this box if your study does not involve direct intervention or direct interaction with subjects (e.g., record-review research, secondary data analysis). (you will not need to answer the impaired consent capacity questions)

Does this study focus on adult subjects with any of the clinical conditions listed below that present a high *likelihood* of impaired consent capacity or *fluctuations* in consent capacity? (see examples below)

○ Yes ◉ No

If Yes, go to the following link and complete and attach the indicated form unless you are filing for an exemption certification: https://ris.uky.edu/ori/oriforms/formt/Scale.asp

Examples of such conditions include:

- Traumatic brain injury or acquired brain injury
- Severe depressive disorders or Bipolar disorders
- Schizophrenia or other mental disorders that involve serious cognitive disturbances
- Stroke
- Developmental disabilities
- Degenerative dementias
- CNS cancers and other cancers with possible CNS involvement
- Late stage Parkinson's Disease
- Late stage persistent substance dependence
- Ischemic heart disease
- HIV/AIDS
- COPD
- Renal insufficiency
- Diabetes
- Autoimmune or inflammatory disorders
- Chronic non-malignant pain disorders
- Drug effects
- Other acute medical crises

Attachments

INFORMED CONSENT/ASSENT PROCESS/WAIVER

For your informed consent attachment(s), please download the most up-to-date version listed in "All Templates" under the APPLICATION LINKS menu on the left, and revise to be in accord with your research project.

Additional Resources:

- Sample Repository/Registry/Bank Consent (PDF) (Word)
- Instructions for Proposed Informed Consent Document
- Instructions for Proposed Assent Form

Consent/Assent Tips:

- **If you have multiple consent documents, be sure to upload each individually (not all in a combined file).**
- **Changes to consent documents (e.g., informed consent form, assent form, cover letter, etc...) should be reflected in a 'tracked changes' version and uploaded separately with the Document Type "Highlighted Changes".**
- **It is very important that only the documents you wish to have approved by the IRB are attached; DELETE OUTDATED FILES -- previously *approved* versions will still be available in Protocol History.**
- **Attachments that are assigned a Document Type to which an IRB approval stamp applies will be considered the version(s) to be used for enrolling subjects once IRB approval has been issued.**
  Document Types that do NOT get an IRB approval stamp are:
  - **"Highlighted Changes",**
  - **"Phone Script", and**
  - **"Sponsor's Sample Consent Form".**

How to Get the Informed Consent Section Check Mark

1. **You must check the box for at least one of the consent items and/or check mark one of the waivers, then if applicable attach the corresponding document(s) as a PDF (if open to enrollment).**
2. **If you no longer need a consent document approved (e.g., closed to enrollment), or, the consent document submitted does not need a stamp for enrolling subjects (e.g., umbrella study, or sub-study), only check mark the "Stamped Consent Doc(s) Not Needed".**
3. **After making your selection(s) be sure to scroll to the bottom of this section and SAVE your work!**

Check All That Apply

- ☐ Informed Consent Form (and/or Parental Permission Form)
- ☐ Assent Form
- ☐ Cover Letter (for survey/questionnaire research)
- ☐ Phone Script
- ☑ Informed Consent/HIPAA Combined Form
- ☐ Debriefing and/or Permission to Use Data Form
- ☐ Sponsor's sample consent form for Dept. of Health and Human Services (DHHS)-approved protocol
- ☐ Stamped Consent Doc(s) Not Needed

Attachments

Attach Type	File Name
Informed ConsentHIPAA Combined Form	Screening consent CLEAN 8.26.2019.pdf
Informed ConsentHIPAA Combined Form	clean Extended Treatment Consent 9.3.2019 pdf.pdf
Informed ConsentHIPAA Combined Form	treatment consent 1.30.20 clean.pdf

☐ Request for Waiver of Informed Consent Process

If you are requesting IRB approval for waiver of the requirement for the informed consent process, or alteration of some or all of the elements of informed consent (i.e. medical record review, deception research, or collection of biological specimens), complete Section 1 and Section 2 below.

Note: The IRB does not approve waiver or alteration of the consent process for greater than minimal risk research, except for planned emergency/acute care research as provided under FDA regulations. Contact ORI for regulations that apply to single emergency use waiver or acute care research waiver (859-257-9428).

SECTION 1.

Check the appropriate item:

☐ I am requesting waiver of the requirement for the informed consent process.

☐ I am requesting alteration of the informed consent process.

If you checked the box for this item, describe which elements of consent will be altered, and/or omitted, and justify the alteration.

SECTION 2.

The IRB may consider your request provided that **all** of the following conditions apply to your research and are appropriately justified. Explain in the space provided for each condition how it applies to your research.

a) The research involves no more than minimal risk to the subject.

b) The rights and welfare of subjects will not be adversely affected.

c) The research could not practicably be carried out without the requested waiver or alteration.

d) Whenever possible, the subjects or legally authorized representatives will be provided with additional pertinent information after they have participated in the study.

Request for Waiver of Documentation of Informed Consent Process

If you are requesting IRB approval for waiver of the requirement for documentation of informed consent (i.e. telephone survey or mailed survey, internet research, or certain international research), **your research activities must fit into one of three regulatory options**:

1. The only record linking the participant and the research would be the consent document, and the principal risk would be potential harm resulting from a breach of confidentiality (i.e., a study that involves participants who use illegal drugs).
2. The research presents no more than minimal risk to the participant and involves no procedures for which written consent is normally required outside of the research context (i.e. a cover letter on a survey, or a phone script).
3. The participant (or legally authorized representative) is a member of a distinct cultural group or community in which signing forms is not the norm, and the research presents no more than minimal risk to the subject and there is an appropriate alternative mechanism for documenting that informed consent was obtained.

Select the option below that best fits your study, and explain in the space provided how your study meets the criteria for the selected regulatory option.

Note: The IRB cannot waive the requirement for documentation or alter the consent form for FDA-regulated research unless it meets Option #2 below. FDA does not accept Option #1.

Note: Even if a waiver of the requirement for documentation is approved by the IRB, participants must still be provided oral or written (e.g., cover letter) information including all required and appropriate elements of consent so they have the knowledge and opportunity to consider whether or not to participate. To help ensure required elements are included in your consent document, please use the **Cover Letter Template** as a guide: *English*- [WORD], Spanish- [WORD] The cover letter template was developed specifically for survey/questionnaire research; however, it may be useful as a guide for developing a consent document for other types of research as well.

Option 1

a) The only record linking the participant and the research would be the consent document:

b) The principal risk would be potential harm resulting from a breach of confidentiality (i.e., a study that involves subjects who use illegal drugs).

Under this option, each participant (or legally authorized representative) must be asked whether (s)he wants to sign a consent document; if the participant agrees to sign a consent document, only an IRB approved version should be used.

Option 2

a) The research presents no more than minimal risk to the participant:

b) Involves no procedures for which written consent is normally required outside of the research context (i.e. a cover letter on a survey, or a phone script):

Option 3

a) The subject (or legally authorized representative) is a member of a distinct cultural group or community in which signing forms is not the norm.

b) The research presents no more than minimal risk to the subject.

c) There is an appropriate alternative mechanism for documenting that informed consent was obtained.

STUDY PERSONNEL

Do you have study personnel who will be assisting with the research?
After selecting 'Yes' or 'No' you must save by hitting the 'Save Study Personnel Information' button.

◉ Yes ○ No

Manage Study Personnel

Identify other study personnel assisting in research project:

- The individual listed as PI in the 'PI Contact Information' section should NOT be added to this section.
- If the research is being completed to meet the requirements of a University of Kentucky academic program, the faculty advisor is also considered study personnel and should be listed as such below. ***Residents and students who are PI's are encouraged to designate at least one other individual (e.g., faculty advisor) as a contact with an editor role (DP).***
- Role: DP = Editor (individual can view, navigate, and edit the application for any review phase (IR, CR/FR, MR) or 'Other Review", and submit Other Reviews on behalf of the PI.)
- Role: SP = Reader (individual can view and navigate through the currently approved application only.)

To add an individual via the below feature, search for applicable personnel first, then click "select" by the listing for the person you want to add as study personnel to your protocol. For each individual selected, be sure to specify responsibility in the project, whether authorized by the principal investigator to obtain informed consent, AND denote who should regularly receive E-IRB notifications.

NOTE: Study personnel are required to receive human research protection (HSP) training before implementing any research procedures (e.g., CITI). For information about mandatory training requirements for study personnel, visit UK's FAQ's on Mandatory Training web page, or contact ORI at 859-257-9428. If you have documentation of current HSP training other than that acquired through UK CITI, you may submit it to ORI (Jen.Hill@uky.edu) for credit.

Study personnel assisting in research project:

Last Name	First Name	Responsibility In Project	Role	AC	Contact	Degree	StatusFlag	(HSP)	(HSP)Date	Removed?	Last Updated	SFI
AbouAhmed	Amira	Project Assistance/Support	SP	N	N			Y	10/22/2019	N	12/06/2017	N
Ahmed	Mohamed Tarek Seleem	Data Analysis/Processing	SP	N	N		P	Y	05/12/2019	N	05/20/2019	N
Blomquist	Gustav	Co-Investigator	SP	N	N			Y	01/24/2019	N	12/06/2017	N
Braden	Sabrina	Project Assistance/Support	SP	N	N			Y	10/04/2018	N	12/06/2017	N
Broome	Bibi	Project Assistance/Support	SP	N	N			Y	07/31/2017	N	12/06/2017	N
Chamblin	Lisa	Project Assistance/Support	SP	N	N			Y	08/05/2019	N	12/06/2017	N
Davenport	Daniel	Co-Investigator	SP	N	N			Y	01/03/2018	N	12/06/2017	N
Gupta	Vedant	Data Analysis/Processing	SP	N	N		P	Y	08/20/2019	N	02/07/2020	N
Hellman	Katelyn	Study Coordinator	DP	Y	Y		P	Y	06/07/2019	N	06/11/2018	N
Holbrook	Kathryn	Project Assistance/Support	SP	N	N			Y	12/12/2018	N	12/06/2017	N
Hughes	Nedda	Study Coordinator	DP	Y	Y			N	01/06/2017	N	12/06/2017	N
Kaenzig	Janet	Project Assistance/Support	SP	N	N			Y	09/07/2017	N	12/06/2017	N
Kryscio	Richard	Co-Investigator	SP	N	N			Y	07/18/2019	N	12/06/2017	N
Lima	Florence	Data Analysis/Processing	SP	N	N			Y	10/31/2019	N	12/06/2017	N
McLaughlin	Kimberly	Study Coordinator	SP	N	N			Y	03/22/2017	N	12/06/2017	N
Monier Faugere	Marie	Co-Investigator	SP	N	N			Y	08/17/2017	N	12/06/2017	N
Montgomery	Justin	Co-Investigator	SP	N	N			Y	03/08/2018	N	12/06/2017	N
Nassar	Elias	Data Analysis/Processing	SP	N	N		S	Y	10/03/2019	N	04/26/2019	N
Rice	Linda	Project Assistance/Support	SP	N	N			Y	09/05/2019	N	12/06/2017	N
Richeson	Dianne	Project Assistance/Support	SP	N	N			Y	02/27/2017	N	12/06/2017	N

Last Name	First Name	Responsibility In Project	Role	AC	Contact	Degree	StatusFlag	(HSP)	(HSP)Date	Removed?	Last Updated	SFI
Ross	Dorothy	Project Assistance/Support	SP	N	N			Y	10/04/2018	N	12/06/2017	N
Sexton	Teresa	Project Assistance/Support	SP	N	N			Y	01/03/2020	N	12/06/2017	N
Shelton	Charles	Data Collection	SP	N	N		N	Y	03/03/3000	N	04/23/2019	N
Spach	Tara	Study Coordinator	DP	Y	Y			Y	12/23/2019	N	12/06/2017	N
Spear	Terri	Project Assistance/Support	SP	N	N			Y	05/22/2018	N	12/06/2017	N
Tillery	Melanie	Project Assistance/Support	SP	N	N			Y	01/10/2019	N	12/06/2017	N
Walker	Kaitlin	Study Coordinator	DP	Y	Y		P	Y	12/04/2019	N	12/05/2019	N
Winkler	Michael	Co-Investigator	SP	N	N			Y	03/27/2017	N	12/06/2017	N

RESEARCH DESCRIPTION

****!!!PLEASE READ!!!** Known Issue: The below text boxes do not allow symbols, web addresses, or special characters (characters on a standard keyboard should be ok). If something is entered that the text boxes don't allow, user will lose unsaved information.**

Workaround(s):

- **Save your work often to avoid losing data.**
- **Use one of the attachment buttons in this section, or under the Additional Information section to include the information with your application. During the document upload process, you will be able to provide a brief description of the attachment.**

Background: Provide an introduction and background information. Describe past experimental and/or clinical findings leading to the formulation of your study. For research involving investigational drugs, describe the previously conducted animal and human studies. You may reference grant application/sponsor's relevant protocol pages and attach as an appendix in the E-IRB "Additional Information" section, however, a summary paragraph must be provided in the text box below. For research that involves FDA approved drugs or devices, describe the FDA approved uses of this drug/device in relation to your protocol. Attach a copy of the approved labeling as a product package insert or from the Physician's Desk Reference in the applicable E-IRB "Study Drug" or "Study Device" section.

Background: Chronic kidney disease (CKD) is a pervasive health problem affecting more than 10% of the general population of the U.S., 31.7 million individuals.1, 2 Chronic kidney disease bone and mineral disorder (CKD-MBD) starts early during the loss of kidney function and is seen in virtually all CKD stage 5 patients.3 Bone loss is an integral part of renal osteodystrophy (ROD) which encompasses the bone abnormalities of CKD-MBD.4, 5 Our prior funding period study revealed the important findings that 30% of CKD-5D patients are osteoporotic, and that over 33% of these patients have substantial bone loss over a one year6. Bone loss of the hip measured by quantitative computed tomography (QCT) showed the most severe losses. It is of note that hip fractures occur in patients with CKD-MBD at a rate that is up to 10 times higher than in the general population;7-12 with an associated high cost and morbidity. These fractures occur 10-15 years earlier than in non-CKD patients and have an annual subsequent mortality of 64%.8 Additionally, CKD patients with osteopenia are at greater risk for an exponential rate of bone loss than already osteoporotic patients.

However, despite these devastating outcomes, there are no FDA approved therapies for CKD-associated osteoporosis low bone density, or bone loss. Consequently, CKD-associated bone lossosteoporosis is rarely treated by practicing nephrologists. Exacerbating the treatment challenges is the fact that CKD- bone lossosteoporosis distinctly differs from post-menopausal low bone densityosteoporosis. The primary mechanism of bone loss in post-menopausal osteoporosis is increased bone resorption, while in CKD- bone lossosteoporosis, the primary mechanism of bone loss is suppressed bone formation in patients with low bone turnover as opposed to excessive bone resorption in patients with normal or high bone turnover.13-17 At this time, there is no uniform treatment protocol that differentiates between low and high turnover patients. Available reports describe small numbers of patients treated for short time periods18-25 without distinction between bone turnover states and undesirable effects are observed when treatment modalities are not individualized based on turnover.18, 24, 26 This study will provide proof of concept that an individualized treatment approach to bone lossosteoporosis in CKD-5D is beneficial for reversing bone loss.
In an analysis of 630 bone biopsies from adult CKD-5D patients, we found that prevalence and diagnostic thresholds for turnover identification differed between white and black patients.15 These data called for race specific algorithms for determination of low and high bone turnover which we developed using classification and regression tree (CART) analyses of total parathyroid hormone (PTH) and PTH ratios versus histologically determined turnover state.27, 28 These results were complemented by the findings of a predictive value of tartrate resistant acid phosphatase-5b (TRAP-5b) for assessment of turnover 29-31 resulting in the race-specific low turnover identification algorithm shown in Table 1.
The prime therapeutic approach for post-menopausal bone lossosteoporosis using antiresorbers would be detrimental if applied to CKD-MBD patients with low bone turnover. Bisphosphonates, the most frequently used antiresorbers for treatment of bone lossosteoporosis, have a suppressive effect on bone turnover and their half-life in bone is 6-10 years. If given to a CKD-5D patient with low bone turnover, they may induce adynamic bone disease with its known negative effects on mineral homeostasis, vascular calcifications32, 33 and fractures.8 Bisphosphonates might be effective in patients with normal or high turnover, but a different drug is needed to treat low turnover patients. Teriparatide is the only available FDA-approved drug for low turnover patients. It is the active PTH 1-34 fragment, and has been shown in low bone densityosteoporotic non-CKD patients to stimulate bone turnover and increase bone mass if given in daily doses creating active PTH spikes.34-36 In CKD-5D patients, the high levels of endogenous PTH include a large portion of active and non-active PTH fragments, which might dilute or hinder the formation of these active spikes and thus negate the therapeutic effect. Indeed, it has been shown that teriparatide treatment alone in CKD-5D patients with elevated serum PTH does not result in increases in bone formation markers.25 Control of PTH over-secretion will overcome these problems and allow the relatively small doses of teriparatide to exert their effects. It has been shown that cinacalcet treatment effectively suppresses both active as well as non-active PTH in over 200 CKD-5D patients.37 We have collected preliminary data in six CKD-5D patients with low bone densityosteoporosis diagnosed by dual-energy X-ray absorptiometry (DXA). These patients were treated with teriparatide combined with cinacalcet to suppress endogenous PTH to levels less than 200 pg/mL. We found that the combination of the two drugs resulted in the desired sustained suppression of intact PTH over a period of up to two years and increased bone formation markers. Figure 1 shows an example of a 63-year old woman with CKD-5D who had a femur fracture and osteoporotic T-scores by DXA (hip T-score = -5.6; spine T-score = -2.6). Her bone biopsy showed low turnover bone disease. She was treated with teriparatide 20 µg daily injections combined with cinacalcet 30 mg per day. With this regimen, we were able to maintain PTH levels at or below 200 pg/mL and to document an increase in bone formation markers after two years (Figure 1). BMD measured by DXA showed a significant increase in the T-score (hip -5.6 to -2.5; spine -2.6 to -1.9). She had a dramatic improvement in physical activity and no longer required assistance while walking. The other five patients with CKD-associated bone lossosteoporosis were treated

with teriparatide combined with cinacalcet for up to six months. Their PTH levels were maintained at <200 pg/mL, and the bone formation markers bone specific alkaline phosphatase (BSAP) and osteocalcin increased by more than 100%. In the proposed study, we will follow BSAP and procollagen type 1 N-terminal propeptide (P1NP) which are not renally excreted; osteocalcin will not be followed because it is retained in CKD. In one of the six patients, bone biopsies were performed before and after six months of treatment and a significant increase in bone formation rate was observed. Independent of us, a patient with adynamic bone disease by bone histology treated with teriparatide for one year was presented at the American Society for Bone and Mineral Research 2014 Annual Meeting. Cinacalcet was not given because serum PTH levels were very low. An increase in trabecular bone volume and bone formation parameters was demonstrated by bone histomorphometry (P. Miller, personal communication).
Coronary, aortic and valvular calcifications (CAVC) are also an integral part of CKD-MBD. They are associated with increased risk for cardiovascular events,24, 25 and are seen in patients with low bone mass regardless of turnover state.17, 18, 26, 27 During our prior funding period we demonstrated that bone lossosteoporosis is a predictor of more severe progression in coronary artery calcification (CAC) in CKD-5D patients. In non-CKD post-menopausal women, there is more progression in vascular calcification when bone loss is more severe.42 In low bone turnover mice with CKD-MBD teriparatide treatment resulted in increased bone mass, decreased vascular calcification, and reduction in cardiac valve calcification.43 In diabetic low-density lipoprotein receptor-deficient mice with low bone turnover, teriparatide treatment reduced cardiac valve calcification by 80%.43 In uremic rats, treatment with bisphosphonates inhibited aortic calcification44, 45, and in warfarin treated rats, alendronate and ibandronate inhibited calcifications in all arteries and heart valves.46 We therefore expect a reduction of CAVC progression under the proposed treatments which may be linked to bone changes or may be a parallel independent pathogenetic process. Thus, even if the bone changes of the first specific aim are not observed, it is not unreasonable to expect reduction in CAVC progression under treatment in support of specific aim #2.
Along with changes in BMD and CAVC, whole body DXA scans will be performed to assess total body composition (%fat vs. % lean). Previous studies have reported an increase in survival in CKD-5D patients with higher lean body mass.
We will also measure fibroblast growth factor 23 (FGF23), indicators of Wnt pathway activity and markers of bone resorption and formation. Our one year study in 122 CKD-5D patients treated according to standard of care (Kidney Dialysis Improving Global Outcomes guidelines47) showed an increase in FGF23 (5210 to 9349 RU/mL, $p<0.001$), sclerostin (1148 to 2060 pg/mL, $p<0.001$) and Dickkopf 1 (DKK1) (24 to 33 pmol/L, $p<0.015$); and a decrease in P1NP (36 to 16.4 ng/mL, $p<0.001$) (Resubmitted to JASN). Analysis of these parameters in the proposed study with specific anti-osteoporosis treatments will give valuable new signals regarding mechanisms for the bone and CAVC changes we expect to observe. This will include information on potential treatment effects of FGF23.
This phase II proof of concept study will demonstrate that a novel individualized treatment regimen for low bone densityosteoporosis in CKD-5D patients which differentiates patients by bone turnover status. Proof of this innovative concept is expected to set the stage for a Phase III trial which would provide the first CKD-associated osteoporosis treatments for approval by the FDA. Proof of concept will shift current clinical practice paradigms towards treatment and prevention of CKD-MBD bone lossosteoporosis. This is of great health relevance because at this time low bone densityosteoporosis in CKD-5D patients is not even evaluated, much less treated. Moreover, the study is expected to provide new information on whether such treatment may also retard the relentless progression of vascular calcification and whether changes in bone markers can predict the expected therapeutic results.
The study regimen includes a novel appreciation of the different PTH thresholds for identification of turnover states in black versus white patients. Turnover in black patients is more difficult to assess than in white patients and this has been an additional barrier to the willingness to treat bone lossosteoporosis in CKD-5D patients. The results obtained during our prior funding period have provided us a novel and solid base for non-invasive assessment of bone turnover in blacks and white patients used in this protocol.
The proposed study uses a novel medication regimen, i.e., concomitant cinacalcet use, to make teriparatide effective in these patients. Teriparatide treatment alone in CKD-5 D patients with low turnover bone lossosteoporosis and elevated PTH does not result in an increase in bone formation markers.25
This study will provide innovative targeting of bisphosphonates to the normal to high turnover CKD-5D patient population. There are a few uncontrolled studies of bisphosphonate treatment in CKD-5D but these do not separate high from low bone turnover.19, 21-23
This study will produce new data indicating whether these treatments will retard the relentless progression of CAVC in CKD-5D patients associated with the cardiovascular events responsible for mortality rates exceeding many cancers.
Moreover, new insights will be gained into the specific links between bone and CAVC outcomes and FGF23, indicators of Wnt pathway and markers of bone formation and resorption.
Upon completion of the study, we will, for the first time, make it possible to effectively manage CKD-associated bone lossosteoporosis in both black and white patients.

Objectives: List your research objectives. You may reference grant application/sponsor's relevant protocol pages and attach as an appendix in the E-IRB "Additional Information" section, however, a summary paragraph must be provided in the text box below.

Specific Aim #1: Evaluate a novel individualized treatment regimen for low bone densityosteoporosis in CKD-5D patients. For this purpose, CKD-5D patients with established low bone densityosteoporosis will be enrolled into one of two treatment arms based on bone turnover status; low versus normal-high. Each arm will be randomized into treatment or control groups. In the low turnover arm, teriparatide combined with cinacalcet will be given to stimulate bone formation, and in the normal-high turnover arm, alendronate will be administered to reduce bone resorption. We will monitor safety and response by patient assessments and blood draws at regular visits and telephone calls. The primary endpoint for Specific Aim #1, bone mineral density (BMD), will be measured by quantitative computed tomography (QCT) at baseline, 6 months and after one year and two years of treatment.
Specific Aim #2: Evaluate the effects of the above treatments on CAVC progression (secondary endpoint) measured using multi-detector computed tomography (MDCT) at baseline, 6 months and after one and two years of treatment.
Other Secondary Endpoints: Bone serum biochemical parameters obtained at quarterly monitoring visits: FGF23, sclerostin, DKK1, PTH, the PTH 1-84/PTH N-terminal truncated fragment ratio, TRAP-5b, BSAP, and P1NP.
Analyses will also be performed to identify links between the response of these serum biochemical parameters to the treatments and changes in bone mass and CAVC. These data should provide novel information on potential mechanisms for both bone loss and CAVC progression.
This study is a logical continuation of our NIH funded studies that have established the severity of bone loss in CKD-5D patients and its association with vascular calcifications. These severe clinical problems have major morbidity and mortality and are routinely

untreated. The results of this study will provide proof of concept for a greatly needed low bone densityosteoporosis treatment regimen by differentiating turnover status and race in CKD-5D patients.

Study Design: Describe the study design (e.g., single/double blind, parallel, crossover, etc.). Indicate whether or not the subjects will receive placebo medication at some point in the research procedures. Also, indicate whether or not the subjects will be randomized in this study. You may reference sponsor's protocol pages and attach as an appendix in the E-IRB "Additional Information" section, however, a summary paragraph must be provided in the text box below. (Including the study design table from a sponsor's protocol is helpful to IRB members.)

Community-Based Participatory Research: If you are conducting community-based participatory research (CBPR), describe strategies for involvement of community members in the design and implementation of the study, and dissemination of results from the study.

Research Repositories: If the purpose of this submission is to establish a Research Repository (bank, registry) indicate whether the material you plan to collect would or would not be available from a commercial supplier, clinical lab, or established IRB approved research repository. Provide scientific justification for establishment of an additional repository collecting duplicate material. Describe the repository design and operating procedures. For relevant information to include, see the UK Research Biospecimen Bank Guidance [PDF] or the UK Research Registry Guidance [PDF]

Patient recruitment will be done for the first 42 months of the study after administrative startup (Figure 2). Biochemical measurements, MDCT, QCT and DXA scans, and clinical assessment will be performed at baseline, 6 months, and at 12 months, 18 months and 24 months. Treatment monitoring visits with blood draws (initially bi-weekly or monthly and thereafter every 3 months) and adverse event monitoring phone calls (monthly at least) will occur during years one through five. Interim analyses and first publications will be done once 50% of patients have completed 1 year visits, approximately at the end of Year 3. Final analyses of the data and preparation of abstracts and manuscripts of the obtained results will be completed during year 5. Control patients who completed 1 year of follow up without treatment will be offered additional 2 years of enrollment with treatment according to protocol. Patients who were initially randomized to treatment groups will be offered continued treatment for an additional 1 year to complete 2 years of therapy. Previously enrolled patients will be recruited from the beginning of patient enrollment. These patients will be provided with an additional consent for the extension of the treatment arm.
Figure 2: Study Timeline

Serum Biochemical Parameters. Blood draws and laboratory analysis will be performed by the Center for Clinical and Translational Science (CCTS). Blood specimens may also be obtained in tubes by the dialysis staff, for pick up by the coordinators, at the time the patient is receiving dialysis to minimize additional patient venipuncture. Serum calcium will be measured using routine laboratory technique (Roche autoanalyzer). Plasma intact and 1-84 PTH levels will be measured by a radioimmunometric assay (Scantibodies, Santee, CA). The intra- and interassay coefficients of variation for intact PTH are <5 and <7%, and for 1-84 PTH <6 and <8%. BSAP levels will be measured using an EIA (Metra BAP EIA, Quidel, San Diego, CA). The intra- and inter-assay coefficients of variation are <6% and <8%. TRAP-5b levels will be determined using an EIA (MicroVue, Quidel, Santa Clara, CA). The intra- and inter-assay coefficients of variation are <2.2% and <3%. P1NP levels will be measured using an ELISA (USCNK, Wuhan, China); the intra- and inter-assay coefficients of variation are <9% and <10%. Serum sclerostin levels will be measured using an EIA (Tecomedical group, Sissach, Switzerland). The intra- and inter-assay coefficients of variation are <3.1% and <3.5%. Serum FGF23 levels will be measured by an ELISA (EMD Millipore, Billerica, MA). The intra- and inter-assay coefficients of variation are <8% and <12%. DKK1 will be determined by an ELISA (Biomedica, Vienna, Austria). The intra- and inter-assay coefficients of variation are <8% and <12%. Bone mineral density (BMD) Two techniques—DXA and QCT—will measure BMD. DXA measurements will be performed in the CCTS core facility. QCT measurements will be conducted in the UK Department of Radiology and qualitatively analyzed on a Syngo MMWP workstation and quantified in the Image Analysis Lab of the Division of Nephrology, Bone and Mineral Metabolism. Measurements will be performed using FDA approved imaging equipment, calibration phantoms, and post imaging analysis software/clients used in everyday clinical practice. (The medical center is on a regular schedule of equipment upgrades and, consequently, the specific equipment utilized will change periodically.) Imaging equipment will be maintained and calibrated using manufacturer recommended techniques and schedules. The studies will be performed under the supervision of, and interpreted by, board certified physicians.

Daily calibration scans will be obtained according to the manufacturer's recommended procedure. Quarterly, an entire calibration suite of checks will be performed and recorded. These tests include phantom measurements of signal-to-noise, contrast-to-noise, and spatial and gray-scale resolution. Every 2 weeks, quality assurance scans of a QCT phantom will be performed at the CT scan site. The precision of the QCT measurements is 0.8%. If the individual phantom readings are more than 3% of the mean value, then the field engineers will service the CT scanner.
Dual Energy X-ray Absorptiometry (DXA) (GE Lunar iDXA, Madison, WI) will be performed according to the manufacturer's recommendations for patient positioning, scan protocols, and scan analysis. Measurements of the spine and hip will be obtained from the AP projection. Bone mineral density and bone mineral content (BMC) results are analyzed for individual vertebrae as well as for the mean of L1-L4. BMD and BMC are measured and aggregated for the right and left total hip regions. In addition, measurements of the distal radius (33%) will be obtained. The coefficients of variation for these BMD measurements are: AP spine, 1.35% and total hip, 0.52%, radius 1.20%. Total body scans will be performed to assess body composition (%fat vs. % lean). It is anticipated that for the duration of the study, the same operator will use the same machine.
Daily quality-control scans are obtained with Lunar's anthropomorphic phantom. If results are more than 2 standard deviations (SD) from baseline, we will repeat the phantom scan. If the results of both scans are greater than 2 SDs from baseline, we will not measure additional patients before the scanner is serviced. Each week, the daily phantom data are analyzed to detect drifts. In the event of scanner maintenance, precision studies are performed to ensure consistency of measurement.

Coronary, Aortic and Valve Calcification (CAVC): CAVC will be assessed using MDCT. Non-contrast computed tomography will be performed on a 64 Slice Dual Source CT Somatom Definition scanner (Siemens AG, Erlangen, Germany). Images will be acquired from 3cm above the aortic arch to 2 cm below the heart. Scan parameter are the following: non-ECG gated 64 x 0.6 collimation, 120 kVp, quality reference mass 160mAs, 0.33 sec gantry rotation time (QUICK) and 3 mm slice thickness. Images will be analyzed on a 3D workstation using calcium scoring software (HeartView CT, Siemens AG, Erlangen, Germany). Calcifications are identified as a plaque of =1 mm2 with a density of =130 HU and quantified using the previously described Agatston scoring method.53 Intra and inter-observer error for interpretation of images is <1% based on our prior funded studies. Intra-observer error was determined through comparison of repeated interpretation 2-4 weeks apart. In addition same scan inter-observer variability was determined (through repeat measurements 30 minutes apart) to be <1% based on our prior funded studies.
CAVC will also be determined at baseline, 6 months and at one year intervals using the square root of volume (CAVC SRV) an analytic method that accounts for interscan variability,54, 55 and CAVC density. We will calculate the area of the plaque by dividing the CAVC volume by the thickness of the slice (3 mm). Density will then be calculated by taking the Agatston score divided by the area.39 Some patients will have coronary artery and vascular stents, coronary artery bypass changes, intraluminal catheters and automated implantable cardioverter-defibrillators. In patients with coronary artery stents, the CAVC scores will be obtained both with and without inclusion of the stents. Artifacts from metal or catheters including streak will be excluded by hand while drawing regions of interest. Attempts will be made to scan patients with acceptable heart rates, less than 80-100 bpm, to reduce motion artifact. In the case of coronary artery motion artifact, regions of interest will be drawn to exclude motion oriented inflation of CAVC scores. In severe cases of motion patients will be rescanned. Single rescans are deemed acceptable radiation exposure. Similar daily, weekly and yearly calibration scans will be obtained according to the manufacturer's recommended procedure as discussed in the QCT paragraph above.

Acquisition and Analysis of Cardiovascular Calcification Data: Multirow Detector Array Computed Tomography (a.k.a. Multislice Computed Tomography or MSCT) of multiple vascular territories will be performed to acquire robust data related to aortic and conduit artery calcification (e.g. coronary artery calcium (CAC), thoracic aorta calcium (TAC) and abdominal aorta calcium (AAC) data). Data will be acquired with Siemens Force Scanners (dual source, 192 row detector array) located on the campus of the University of Kentucky Medical Center. Analysis of imaging data will be performed utilizing the advanced post processing clients (e.g. Terarecon, Osirix, Syngo Via, Elucid, 3D slicer) available in the University of Kentucky Department of Radiology clinical and research facilities. Co-investigators from among the Radiology faculty will supervise these processes. If, during these processes, a radiologist makes a clinical observation which, to insure the health and wellbeing of study subjects, merits further investigation, the PI will be promptly informed.

Attachments

Attach Type	File Name
StudyDesign	Form B graph 8.8.2019.pdf

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Study Population: Describe the characteristics of the subject population, such as anticipated number, age range, gender, ethnic background and health status. Identify the criteria for inclusion and exclusion. Explain the rationale for the use of special classes such as fetuses, pregnant women, children, institutionalized, adults with impaired consent capacity, prisoners, economically or educationally disadvantaged persons or others who are likely to be vulnerable.

If women or minorities are included, please address how the inclusion of women and members of minority groups and their subpopulations will help you meet your scientific objectives. Exclusion of women or minorities requires clear and compelling rationale that shows inclusion is inappropriate with respect to the health of the subjects or that inclusion is inappropriate for the purpose of the study. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be excluded routinely from participation in clinical research.

Provide the following information:

- A description of the subject selection criteria and rationale for selection in terms of the scientific objectives and proposed study design;
- A compelling rationale for proposed exclusion of any sex/gender or racial/ethnic group;
- The proposed dates of enrollment (beginning and end);
- The proposed sample composition of subjects.

You may reference grant application/sponsor's relevant protocol pages and attach as an appendix using the below attachment button, however, a summary paragraph must be provided in the text box below.

It is anticipated that 990 CKD-5D patients will be enrolled. The study population will include men and women age 21 years and over from various ethnic backgrounds. The enrollment will be done between January 2015 and January 202119.

TARGETED/PLANNED ENROLLMENT: Number of Subjects
Ethnic Category Sex/Gender
Females Males Total
Hispanic or Latino 15 15 30
Not Hispanic or Latino 480 480 960
Ethnic Category: Total of All Subjects * 495 495 990
Racial Categories

American Indian/Alaska Native
Asian 3 3 6
Native Hawaiian or Other Pacific Islander
Black or African American 225 225 450
White 267 267 534
Racial Categories: Total of All Subjects * 495 495 990

Inclusion Criteria:

• Aged 21 years or older;
• Chronic maintenance dialysis of at least 3 months' duration;
• Mental competence;
• Willingness to participate in the study;
• Normal corrected serum calcium.
• Low bone densityOsteoporosis by DXA scan in any site. (T-score = -1-2.5 for men over age 50 or postmenopausal women, or Z-score = --12.5 for all others).

Exclusion criteria:

• Pregnancy or Breast Feeding;
• Incarceration
• Systemic illnesses or organ diseases that may affect bone (except type 1 or type 2 diabetes mellitus);
• Clinical condition that may limit study participation (e.g., unstable angina, respiratory distress, infections).
• Chronic alcoholism and/or drug addiction;
• Known Paget 's disease of bone;
• Prior external beam or implant radiation therapy involving the skeleton, only if randomized to the Teriparatide treatment
• Participation in a study of an investigational drug during the past 90 days;
• Planning to move out of the area within 1 year of the study;
• Scheduled for renal transplantation
• BMD T-score of the radius less than -3.5 by DXA. (if randomized to teriparatide to avoid the known potential negative effects of teriparatide treatment on BMD of the radius)
• Current treatment with medicines containing digoxin;
• More than 3 CT scans in the prior 12 months (to avoid excessive radiation exposure);
• Planned or anticipated oral surgery within the next 12 24 months;
• Inability to stand or sit upright for at least 30 minutes;
• Treatment within the past 6 months with drugs that may affect bone metabolism including bisphosphonates and teriparitide (except for treatment with calcitriol, Vit D analogs and/or calcimimetics).
• Abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia;
• Calcidiol levels below the normal range. The current routine clinical practice in our dialysis clinics is to check calcidiol status twice yearly and supplement with vitamin D according to serum calcidiol levels. It is therefore unlikely that a substantial number of patients will be excluded due to this exclusion criterion.

Attachments

Subject Recruitment Methods & Privacy: Using active voice, describe plans for the identification and recruitment of subjects, including how the population will be identified, and how initial contact will be made with potential subjects by those having legitimate access to the subjects' identity and the subjects' information.

Describe the setting in which an individual will be interacting with an investigator or how and where members of the research team will meet potential participants. If applicable, describe proposed outreach programs for recruiting women, minorities, or disparate populations as participants in clinical research. Describe steps taken to minimize undue influence in recruiting potential participants.

Please note: Based upon both legal and ethical concerns, the UK IRB does not approve finder's fees or "cold call" procedures made by research staff unknown to the potential participant.

For additional details, see topic "Recruitment of Subjects/Advertising" on ORI's IRB Survival Handbook web page and the PI Guide to Identification and Recruitment of Human Subjects for Research [PDF].

Subject Recruitment Methods and Privacy: The study coordinators will visit the patients at the dialysis clinics during their regular treatment hours. The nephrologists at these clinics have worked with us on previous research activity and are willing to cooperate. Patients will be informed about the goals and the protocol of the study. An IRB approved recruitment flyer will be given to patients who are interested in participating in the study. A list of screened patients will be kept under lock and key in the study coordinators' office and on a password protected computer.

The study coordinators will approach via phone during normal business hours all patients who completed study participation and those currently enrolled in ROD III to discuss the extended enrollment option. All previous patients will be eligible for approaching for the extension regardless of when initial participation was completed. Patients will be informed about the goals and the protocol of the study. A list of screened patients will be kept under lock and key in the study coordinators office and on a password protected computer.

Advertising: Specify if any advertising will be performed. If yes, please see "IRB Application Instructions - Advertisements" for instructions on attaching copies of the information to be used in flyers or advertisements. Advertisements must be reviewed and approved by the IRB prior to use. For additional details, see topic "Recruitment of Subjects/Advertising" on ORI's IRB Survival Handbook web page for the *PI Guide to Identification and Recruitment of Human Subjects for Research* [D7.0000] document [PDF]. If you will be recruiting subjects via advertising at non-UK owned or operated sites, you should include a copy of written permission from that site to place the advertisement in their facilities.

Note: Print and media advertisements that will be presented to the public also require review by UK Public Relations (PR) to ensure compliance with UK graphic standards, and equal opportunity language.

Print advertisements: The study may recruit subjects through flyers, brochures, posters, cards for clinic rooms, Research Spotlights, bookmarks placed on campus and in the surrounding community and region, including but not limited to the UK Medical Center, UK Clinics, Good Samaritan Hospital, student center, UHS, the 5 UK Center for Clinical and Translational Research wall mounts, Cardinal Hill, monitor screens, and area facilities and businesses.
This study may use physician referral letters to community physicians for patient recruitment.
Paid print advertising: Subjects may be recruited through paid print advertisements, including brochures, magazines, newspaper (e.g., Herald Leader, Bluegrass Area, Courier Journal, Cincinnati Enquirer, Health & Wellness, Chevy Chaser, Hamburg Journal, Business Lexington, or other publications in the surrounding region), radio (e.g., Sirius, Clear Channel, Cumulus, LM Communications, Public Radio, etc.), television spots, or scrolling information on community stations. Recruitment ads may also appear on billboards, Lextran buses, taxicabs, and other transportation methods.
Internet and Social Media: This study may be advertised on internet webpages (e.g., UKclinicalresearch.com, ResearchMatch.org, CenterWatch, CISCRP, Craig's List, Lexington.MD, UK, CCTS) and may utilize Google Adwords. The study may be promoted via social media, including Facebook boost ads, UK_CCTS Facebook, UK_CCTS Twitter, UK and UKHC social media, and departmental/lab pages. If advertised on UKClinicalresearch.com, the study flyer will include an option for interested individuals to enter and submit their contact information so that principal investigators or research coordinators can contact potential volunteer about participating. Internet and social media recruitment will follow the terms of use for each site utilized.
E-Newsletters and ListServs: This study may also go out on email distribution, listservs, or e- newsletters, e.g., the CCTS list serv, Markey Cancer Affiliates list servs, ResearchMatch.org, Wednesday's Word, KORH, ATRN, etc.
Research Participant Registries: Potential participants may be identified from registry databases, including but not limited to ResearchMatch.org*, Women's Health and You (formerly KY Women's Health Registry), Sanders Brown Center on Aging, Infectious Disease, Dentistry, and the Markey Cancer Center. Databases may also be owned and operated by non-UK research groups (e.g. partnering groups and Health-related Associations).
*ResearchMatch.org will be utilized as a recruitment tool for this protocol. ResearchMatch.org is a national electronic, web-based recruitment tool that was created through the Clinical & Translational Science Awards Consortium in 2009 and is maintained at Vanderbilt University as an IRB-approved data repository (see IRB #090207)." Once UK IRB approval is obtained, a flyer with no contact information will be sent from researcher or designee (proxy) by email to selected de- identified participants in the ResearchMatch registry. If the de-identified participant selects "Yes, I'm interested!" the researcher or proxy will receive information about participant and they may contact them with more information about their research study. If the participant selects "No, thanks", researcher or proxy will not receive any information from de-identified participant.
REDCap prescreening form: The study will employ a pre-screening eligibility survey to determine if a volunteer meets basic inclusion/exclusion criteria (see Appendix _). We will build and administer the eligibility survey on UK's REDCap which provides HIPAA compliant storage on UK servers and encrypted transmission of survey responses. The portable devices do not download the data, it is directly stored into the secure web based connection (https) behind the firewall. All files are password protected once entered into the system. All project data is stored and hosted locally. A link to the eligibility survey will be provided in recruitment materials. The link will also be included in study information sent to ResearchMatch participants who have indicated interest in the study. Before redirecting the volunteer outside of ResearchMatch and to the REDCap survey, the volunteer is once again asked to confirm their interest in completing the pre-screening survey.

Outreach activities: The CCTS attends outreach activities to promote research participation in general (e.g., Roots & Heritage Festival, Latino Festival, Eastern University, Transylvania Health fairs, etc.) and often brings flyers of studies that are currently enrolling participants.
UK Public Relations (College/Dept. PR personnel) and UK HealthCare venues: Articles and inteviews about the researchers and research study may be promoted via UKNow, health columns in the Lexington Herald Leader or Kentucky living, and other media outlets. The study may also be promoted through UKPR and UHC social media webpages (Facebook and UK Twitter), and these posts may also use "boosts" to reach a larger audience. Research and study-related articles published on UKNow may contain standard language directing interested individuals on where to read more about research and current studies: You can make a difference through participating in research and discovery. To find more information, including a list of current studies at UK and access to studies nationwide, please visit UKclinicalresearch.com or call 859.257.7856 or join the ResearchMatch.org register to be matched today.
UKPR and UK HealthCare marketing may create videos to promote research, researchers and their studies to local, regional and national media venues and on internal hospital monitors.
UK HealthCare may place study recruitment flyers on their internal and external racks (e.g., UK pharmacies, clinics, UK Libraries and Lexington Libraries) or on digital monitors.
Participants may be recruited using newsletters, such as In the Loop, Health Matters, Making a difference, and external news letters.
The study may also be advertised through UKPR and UKHC outreach activities. UKHC and CCTS have booths at many events, and researchers and coordinators are invited to attend any events that pertain to their study populations.
Researchers may participate in radio or TV interviews. General information about their research will be discussed and a phone number or website url for more information will be provided.
Consenting members of the research team and/or consenting participants may be interviewed about the study for print, radio, or

video which may be distributed via the aforementioned activities.
We will ensure that future advertising used during the study will not be implemented until the IRB has reviewed and approved those ads.

Attachments

Informed Consent Process: Using active voice, describe the consent/assent procedures to be followed, the circumstances under which consent will be sought and obtained, the timing of obtaining informed consent, whether there is any waiting period between informing the prospective subject and obtaining consent, who will seek consent., steps taken to minimize the possibility of coercion or undue influence, the method used for documenting consent, and if applicable who is authorized to provide permission or consent on behalf of the subject. Note: all individuals authorized to obtain informed consent should be designated as such in the E-IRB "Study Personnel" section of this application.

Describe provisions for obtaining consent/assent among any relevant special populations such as children (see Children in Research Policy [PDF] for guidance), prisoners (see Summary of Prisoner Regulations [PDF] for guidance), and persons with impaired decisional capacity (see Impaired Consent Capacity Policy [PDF] for guidance). Describe, if applicable, use of specific instruments or techniques to assess and confirm potential subjects' understanding of the nature of the elements of informed consent and/or a description of other written materials that will be provided to participants or legally authorized representatives. If you have a script, please prepare it using the informed consent template as a guide, and submit it on a separate page.

Informed Consent for Research Involving Emancipated Individuals
If you plan to enroll some or all prospective subjects as emancipated, consult with UK legal counsel **when preparing the IRB application and prior to submitting the application to the IRB**. Include legal counsel's recommendations (legal counsel's recommendations may be attached in the E-IRB "Additional Information" section as a separate document, if necessary). For a complete definition of emancipated minors, see the section on *Emancipated Individuals* in the Informed Consent SOP [PDF].

Informed Consent for Research Involving Non-English Speaking Subjects
If you are recruiting non-English speaking subjects, the method by which consent is obtained should be in language in which the subject is proficient. Describe the process for obtaining informed consent from prospective subjects in their respective language (or the legally authorized representative's respective language). In order to ensure that individuals are appropriately informed about the study when English is their second-language, describe a plan for evaluating the level of English comprehension, and the threshold for providing a translation, or explain why an evaluation would not be necessary. For additional information on inclusion of non-English speaking subjects, or subjects from a foreign culture, see IRB Application Instructions for Recruiting Non-English Speaking Participants or Participants from a Foreign Culture.

Research Repositories
If the purpose of this submission is to establish a research repository describe the informed consent process. For guidance regarding consent issues, process approaches, and sample language see the Sample Repository/Registry/Bank Consent Template [PDF]

If interested in the study, patients will be explained all potential risks and benefits by the research coordinators. There are two levels of signed consent. The first will be consent for baseline measurements and the second will be consent for treatment for those who qualify. Upon agreement to participate in the study, patients will not be asked to sign the consent form immediately and will be encouraged to take time to think it over and discuss it as they wish with their primary physician and/or family member. Upon agreement, a written consent form approved by the Institutional Review Board (IRB) will be signed by each patient in the presence of a witness. To avoid the appearance of potential coercion, the PI will not seek consent to participate in the study. He will be available for answering additional questions, if needed, after the informed consent form is signed. One copy of the consent form will be given to the patient, and the original will be stored in the patient's file in the study coordinators' office under lock and key. There will not be emancipated individuals. Only English speaking individuals will be enrolled at this time.

If previously completed or current patients are interested in the enrolling in the extended treatment option, patients will be explained all potential risks and benefits by the research coordinators. A third level of consent will be signed for the extended treatment arm. Upon agreement to participate in the study, patients will not be asked to sign the consent form immediately and will be encouraged to take time to think it over and discuss it as they wish with their primary physician and/or family member. Upon agreement, a written consent form approved by the Institutional Review Board (IRB) will be signed by each patient in the presence of a witness. To avoid the appearance of potential coercion, the PI will not seek consent to participate in the study. He will be available for answering additional questions, if needed, after the informed consent form is signed. One copy of the consent form will be given to the patient, and the original will be stored in the patient's file in the study coordinators' office under lock and key. There will not be emancipated individuals. Only English speaking individuals will be enrolled at this time.

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Research Procedures: Describe the research procedures that will be followed. Identify all procedures that will be carried out with each group of subjects. Differentiate between procedures that involve standard/routine clinical care and those that will be performed specifically for this research project.

We will enroll and consent 990 CKD-5D patients. Patients who meet the selection criteria will be informed about the goals, procedures, and potential risks of the study treatment modalities. It will be emphasized that willingness or unwillingness to participate in any aspect of the proposed studies will not affect the patients' medical care. The protocol will be presented by the study coordinator with support of the PI as needed. Patients will be given ample time (1-2 weeks) to think about and discuss their participation with their primary nephrologist, other treating physicians, or any other persons. There will be threetwo levels of signed consent, the first will be consent for baseline measurements and the second for treatment. The third level of consent is for current patients or those who have completed 1 year of ROD III and wish to enroll in the extended option to complete two years of medication therapy. Demographic and clinical information will be recorded at the time of signed consent.
Patients consenting for baseline measurements will have BMD measurements of the total hip, lumbar spine and radius by DXA and total body scan. We do not use QCT for initial BMD assessment to avoid unnecessary radiation exposure to patients with normal bone mass who will be excluded from the study. Patients who are not do not have low bone densityosteoporotic by DXA T-scores/Z-

scores at any site will be excluded from further participation. Results from our prior funding period study indicate this will be 30% or 178 patients. Those patients who are identified as having low bone densityosteoporotic will have blood draws performed for determination of turnover status (PTH, PTH ratio and TRAP-5b; see Table 1) and baseline biochemical results (serum calcium and BSAP). They will also have BMD measurements of the total hip and spine by QCT, and CAVC measured by MDCT.
Patients will be assigned to one of two treatment arms based on their turnover status: 1) low turnover patients and 2) normal or high turnover patients. For each treatment arm we will use adaptive randomization by group completion rates, age race and gender to assign patients to one of two groups A) treatment, and B) no study treatment (standard of care) controls.

For the extension of treatment modification, we will contact all patients who completed one year in either the treatment or control arms. Patients who previously participated in the treatment arm will be offered an additional 1 year of therapy to complete 2 years of therapy. For patients who previously participated in the control arm, they will be offered 2 years of therapy. Both therapies can be given in two consecutive years, or with a time-gap in-between.
TREATMENT PROTOCOLS:
Low Turnover Groups: Patients with low bone turnover will be randomized to receive daily teriparatide injections with cinacalcet or no study treatment, i.e. standard of care, as controls.
Normal or High Turnover Groups: Patients with normal or high bone turnover will be randomized to receive alendronate or no study treatment, i.e., standard of care, as controls. Teriparitide is not justified in these patients because it might worsen underlying high turnover abnormalities and requires avoidable daily injections.

Treatment Protocol for Teriparatide: Patients with low bone turnover will receive a starting dose of 20 µg teriparatide per day via subcutaneous injections along with 30 mg of cinacalcet p.o. daily in the evening will be added after two weeks if PTH is greater than 200 pg/mL at the first biweekly lab draw. Teriparatide treatment alone in patients with histologically proven low turnover bone disease did not result in an increase in bone formation markers.25 Concomitant treatment with cinacalcet is needed in these patients when intact PTH is above 200 pg/mL. To monitor control of PTH and serum calcium levels we will measure them initially one week +/- 3 days after treatment then at the biweekly monitoring visits at the CCTS and quarterly thereafter. Teriparatide dosage will be adjusted according to changes in serum calcium. If serum calcium is between 10.2 and 11 mg/dL, frequency of injection will be reduced to 5 of 7 days per week (non-injection days should not be consecutive and blood draws for serum calcium should be the morning after an injection day). A follow-up visit with serum calcium check will be scheduled in two weeks +/- 3 days. If at that time calcium levels are still between 10.2 and 11, patients will remain with injections on 5 of 7 days per week. If calcium levels return to below 10.2 mg/dL, daily injections will be reinstituted and quarterly calcium checks will be performed. If serum calcium is greater than 11.0 mg/dL, treatment will be withheld for two weeks at which time serum calcium will be rechecked. If it is between 10.2 and 11.0 mg/dL we will reinstitute treatment at the reduced frequency of 5 of 7 days per week. If calcium remains above 11.0 mg/dL, patients will be referred to their primary nephrologist for workup of their hypercalcemia and excluded from further participation in the study.
To assess response or compliance to teriparatide, BSAP (see Table 2) will be measured bi-weekly until steady-state and quarterly thereafter. If results do not increase at least 8% (largest inter-assay error of this marker) the study coordinators will carefully review with the patients the technique of injections and possible compliance lapses. There are no known critical levels indicating undesirably high response without concomitant hypercalcemia. Patients, and if needed a caregiver, will be trained in the subcutaneous administration of teriparatide according to the manufacturer's guidelines.

Table 2. Detail of Blood Draws for Monitoring Safety and Compliance and Secondary Endpoint Serum Biochemical Parameters
Teriparatide
Treatment Group Base-line Bi-weekly visits until steady state Q1 Visit Q2 Visit Q3 Visit 1 Year 15 mo 18mo 21mo 2 yr
or Safety: Serum Calcium & PTH X X X X X X X X X X
For Compliance: BSAP X X X X X X X X X X
Secondary Endpoints: FGF23, P1NP, Sclerostin, DKK-1 & PTH Ratio X X X X X

Alendronate
Treatment Group Base-line Monthly visits until steady state Q1 Visit Q2 Visit Q3 Visit 1 Year 15 mo 18mo 21mo 2yr
For Safety and Compliance: BSAP X X X X X X X X X X
Secondary Endpoints: Serum Calcium, PTH & PTH Ratio, FGF23, P1NP, Sclerostin, DKK-1 X X X X X
Standard of Care Controls Base-line Q2 Visit 1 Year 15mo 18mo 21mo 2 yr
Secondary Endpoints: All of the above Serum Biochemical Parameters X X X X X
Cinacalcet will be adjusted in 30 mg steps up to a maximum daily dose of 180 mg if needed to keep intact PTH at levels less than 200 pg/mL. If by six weeks, this fails to achieve PTH levels less than 200 pg/mL, patients will be excluded from further study participation. In the rare case where PTH level maintenance requires cinacalcet doses that induce serum calcium levels below 8.5 mg/dL, treatment will cease for two weeks after which calcium will be re-measured. At two weeks if calcium remains below 8.5 mg/dL, patients will be excluded from further participation in the study. If calcium is normalized, cinacalcet will be reinstituted at half of the prior dose. Calcium will be checked again at the next monitoring visit. If at any measurement point PTH levels are less than 60 pg/mL cinacalcet will be withheld and reinstituted if levels are again above 200 pg/mL.

Treatment Protocol for Alendronate: Patients with normal or high bone turnover will receive a starting dose of 35 mg alendronate p.o. once per week. Patients will be carefully instructed to follow the manufacturer's recommendations for administration. Serum calcium will be rechecked 1 week +/- 3 days after starting therapy. Dosage will be adjusted according to changes in the bone turnover marker

BSAP from blood drawn at monthly monitoring visits for the first 3 months, thereafter at quarterly monitoring visits. BSAP is expected to go down, but to avoid over-suppression, will not be allowed to go below the low normal range of the assay, as is done clinically. Our data show that mid/normal ranges of these markers in CKD-5D patients indicate low turnover48, 49 If this safety threshold is crossed, treatment will be stopped until values are back above the threshold at a regularly scheduled monitoring visit. Once demonstrably back within safety threshold, treatment will be reinstituted at half of the initial dose (35 mgs every other week). If BSAP does not go down at least 8% over a one month period, treatment doses will be doubled to 70 mgs per week. If they still remain high, study coordinators will carefully review with the patients the mode of drug intake and possible compliance lapses.

Primary Endpoint At one year after baseline, we will assess bone mass using QCT BMD measurements of the total hip and compare 1 and 2 year changes in bone mass between the treatment and control groups. Total hip will be used as the primary endpoint site because in our prior funding period we showed that changes at the total hip in QCT BMD are more pronounced than at the spine6. The Secondary endpoint will be differences between the treatment and control groups in changes in coronary artery calcifications by MDCT. This will be relevant regardless of bone effects.
Other secondary endpoints tracked at baseline, 6 months, and 1 year, 18 and 24 months will include serum biochemical markers of bone activity; FGF 23, BSAP, TRAP5b, P1NP, Sclerostin, and DKK1.
Additionally we will record 1) Change in QCT BMD of the spine to compare with the hip) 2) Changes in DXA BMD of the hip and spine (to determine whether the more commonly available DXA results are equivalent to QCT and 3) Changes in aortic and heart valve calcification (to compare with the coronary artery calcifications).50,51 4)Whole body composition (%fat vs %lean) as it relates to survival in CKD-5D patients.

Attachments

Attach Type	File Name
ResearchProcedures	figure 3 7.22.2019 pdf.pdf

Data Collection: List the data or attach a list of the data to be collected about or from each subject (e.g. interview script, survey tool, data collection form for existing data).

If the research includes survey or interview procedures, the questionnaire, interview questions or assessment scales should be included in the application (use attachment button below).

The data collection instrument(s) can be submitted with your application in draft form with the understanding that the final copy will be submitted to the IRB for approval prior to use (submit final version to the IRB for review as a modification request if initial IRB approval was issued while the data collection instrument was in draft form).

Note: The IRB approval process does not include a statistical review. Investigators are strongly encouraged to develop data management and analysis plans in consult with a statistician.

No data collection instruments will be used in this study.

Attachments

Resources: Describe what resources/facilities are available to perform the research (i.e., staff, space, equipment). Such resources may include a) staffing and personnel, in terms of availability, number, expertise, and experience; b) psychological, social, or medical services, including counseling or social support services that may be required because of research participation; c) psychological, social, or medical monitoring, ancillary care, equipment needed to protect subjects; d) resources for subject communication, such as language translation services, and e) computer or other technological resources, mobile or otherwise, required or created during the conduct of the research. Please note: Some mobile apps may be considered mobile medical devices under FDA regulations (see FDA Guidance). Proximity or availability of other resources should also be taken into consideration, for example, the proximity of an emergency facility for care of subject injury, or availability of psychological support after participation.

Research activities conducted at performance sites that are not owned or operated by the University of Kentucky, at sites that are geographically separate from UK, or at sites that do not fall under the UK IRB's authority, are subject to special procedures for coordination of research review. Additional information is required (see IRB Application Instructions - Off-Site Research web page); supportive documentation can be attached in the E-IRB "Additional Information" section. Provide a written description of the role of the non-UK site(s) or non-UK personnel who will be participating in your research. The other site may need to complete its own IRB review, or a cooperative review arrangement may need to be established. Contact the Office of Research Integrity at (859) 257-9428 if you have questions about the participation of non-UK sites/personnel.

If the University of Kentucky is the lead site in a multi-site study, or the UK investigator is the lead investigator, describe the plan for managing the reporting of unanticipated problems, noncompliance and submission of protocol modifications and interim results from the non-UK sites.

After enrollment by the research coordinators at the dialysis clinics, the study will be conducted at the CCTS for follow up visits, DXA measurements will be performed and blood drawing. CT scans will be done at the Gill CT & MRI Imaging Center, Gill Heart Institute by the certified CT technicians. In the unlikely event that injury occurs during the examinations, the emergency facility is close to both CCTS, and Gill Heart Institute.

Potential Risks: Describe any potential risks or likely adverse effects of the drugs, biologics, devices or procedures subjects may encounter while in the study. Please describe any physical, psychological, social, legal or other risks and assess their likelihood and

seriousness.

Both teriparatide and alendronate have been used in low bone densityosteoporotic patients for more than 11 and 15 years, respectively. In the experience of the PI they are generally well-tolerated. The PI has used these medications in his osteoporosis practice in patients with and without CKD for over 10 years and has experience in long-term monitoring of these treatments.
Alendronate is indicated for the treatment of low bone densityosteoporosis in postmenopausal women and for treatment to increase bone mass in men with bone lossosteoporosis. Alendronate is contraindicated in patients with the following conditions: abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia; inability to stand or sit upright for at least 30 minutes; hypocalcemia, that is, blood calcium levels below normal range for the employed assay; prior hypersensitivity to alendronate. Use of alendronate in CKD-5D patients is not specifically mentioned as a contraindication in the package inserts or on the safety web page. However, it is recommended to not give alendronate to patients with GFR < 35 mL/min. A post-hoc data analysis of 581 women with reduced renal function (GFR < 45 mL/min.) who were participating in the fracture intervention trial showed that alendronate was safe and effective.60
The major observed side effects for alendronate are gastrointestinal complaints which include abdominal pain, nausea, dyspepsia, constipation, diarrhea, and flatulence. Regurgitation, esophageal ulcer, vomiting, dysphagia, abdominal distention, and gastritis have occurred at a lower frequency. Rarely, taste perversion has been reported. The combination of alendronate and naproxen has been reported as synergistic for development of gastric ulcers. The frequency of adverse effects increases with higher dosages. Adverse effects usually have been mild when patients adhered to prescribing instructions. In a 12-week multicenter, randomized, double-blind, placebo-controlled study of 450 post-menopausal women, the incidence of gastrointestinal side effects was comparable (13% vs. 11%) in the treatment and placebo groups.61
Metabolic side effects have included reductions in serum calcium and phosphorus levels as a result of the inhibition of bone resorption. These reductions generally have been mild, asymptomatic, and transient. Musculoskeletal side effects have included bone, muscle or joint pain in approximately 4% of patients. Localized osteonecrosis of the jaw generally associated with tooth extraction and/or local infection has been reported rarely and is likely associated with over-suppression of bone turnover. Also, low-energy femoral shaft and sub-trochanteric insufficiency fractures have been reported in post-marketing experience after long-term use of alendronate (>5 years). Again, over-suppression of turnover is a likely cause.
Teriparatide is indicated: a) for the treatment of postmenopausal women with low bone densityosteoporosis at high risk for fracture, b) to increase bone mass in men with primary or hypogonadal low bone densityosteoporosis at high risk for fracture, and c) for the treatment of men and women with bone lossosteoporosis associated with sustained, systemic glucocorticoid therapy (daily dosage equivalent to 5 mg or greater of prednisone) at high risk for fracture. The risks associated with using teriparatide for treatment of osteoporosis in men and women was assessed in two randomized double blind placebo controlled trials of 1,382 patients, mean age 67 years.71 All-cause mortality, incidence of serious adverse events and discontinuation due to adverse events, were similar or even lower in the teriparatide group. Adverse reactions that were higher in the teriparatide group include: arthralgia, pain, and nausea. Other adverse reactions include dizziness, leg cramps, and injection site reactions. Persistent hypercalcemia is a rare occurrence in these patients. Teriparatide is not used in patients with hypercalcemic disorders and Paget's disease; these are inclusion/exclusion criteria for this study.
The major concern regarding teriparatide treatment is the potential risk for osteosarcoma. There is increased baseline risk for osteosarcoma in patients with Paget's disease of bone, pediatric populations and young adults with open epiphyses, or prior external beam or implant radiation therapy.59 In male and female rats, teriparatide caused an increase in the incidence of osteosarcoma that was dependent on dose and treatment duration. This is why the FDA has limited administration of the drug to a maximum of two years. The observed effect in rats was found with systemic exposures ranging from 3 to 60 times the exposure in humans given a 20 µg dose. The spontaneous occurrence of osteosarcoma in the general population is 1:400,000. At this time, per the manufacturer, more than 1.2 million patients have been treated with teriparatide and three cases of osteosarcoma have been reported.
Cinacalcet is approved for CKD-5D patients. In a double blind placebo controlled trial of cinacalcet in 3,861 patients, there were no differences in serious or non-serious adverse events among the over 1,000 events tracked. This drug is routinely used in daily practice to treat CKD-5D patients for hyperparathyroidism. It may induce hypocalcemia.
The risks associated with blood draws are minimal and restricted to potential discomfort during the procedure and, possibly, soreness, bruising, pain and bleeding at the venipuncture site. In addition, there is a possibility that the patient will faint.
All CT and DXA involve patient exposure to ionizing radiation, but both DXA and CT are generally considered to be safe with relatively low radiation exposure to the patient. Doses involve exposure to the chest, abdomen, and the pelvic region. The yearly safety threshold given by the United States Nuclear Regulatory Commission for occupational radiation exposure is 50 mSv.73 The radiation dose from a typical DXA bone scan produces approximately 1/300th of the natural background radiation dose we receive each year. This radiation dose would not be considered a risk of producing any harmful effects. Each CT scan will give a radiation dose greater than that from typical natural background exposure, but less than the limit for radiation workers and well below the levels that are considered to be a significant risk of any harmful effects.

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Safety Precautions: Describe the procedures for protecting against or minimizing any potential risks, *including risks of breach of confidentiality or invasion of privacy*. Where appropriate, discuss provisions for ensuring necessary medical or professional intervention in the event of adverse events, or unanticipated problems involving subjects. Also, where appropriate, describe the provisions for monitoring the data collected to ensure the safety of subjects. If vulnerable populations other than adults with impaired consent capacity are to be recruited, describe additional safeguards for protecting the subjects' rights and welfare.

Initial Consent Patients will be visited by study coordinators while they are on routine dialysis treatment. Patients who meet the inclusion/exclusion criteria will be informed about the goals, procedures, and potential risks of the study treatment modalities. It will be emphasized that willingness or unwillingness to participate in any aspect of the proposed studies will not affect the patients' medical care. The protocol will be presented by the study coordinator supported by the PI where needed and the patients will be given ample time to think about their participation and to discuss participation with their primary nephrologist, other treating physicians, or any other persons. After verbal agreement to participate, a written first consent form approved by the IRB of the University of Kentucky will be

signed by each patient. Consented patients will have BMD measurements of the total hip, lumbar spine, radius and whole body scan by DXA. We do not perform QCT measurements at this time in order to avoid unnecessary radiation exposure to patients who are not osteoporotic by DXA T-scores at any site because they will not participate any further in the study. Those patients who are identified as having low bone densityosteoporotic will have blood draws performed for determination of bone turnover status and for baseline values of biochemical tests used for monitoring. They will also have BMD measurements of their total hip and spine by QCT, and CAVC measured by MDCT.

Treatment Consent Once bone turnover status has been determined, patients will be approached for the second consent form addressing treatment. It will again be emphasized that willingness or unwillingness to participate in any aspect of the proposed studies will not affect the patients' medical care. The protocol will be presented by the study coordinators supported by the PI where needed and the patients will be given ample time to think about their participation and to discuss participation with their primary nephrologist, other treating physicians, or any other persons. After agreement to participate, the second written treatment consent form approved by the IRB of the University of Kentucky will be signed by each patient. One copy of the first and second signed consent form will be given to the patient; another will be kept in the study coordinators' office under lock and key.

Expanded Consent Patients who have previously completed one year of therapy or standard of care or are currently enrolled will be re-approached for a third consent to extend the treatment so that two years of medication therapy will be completed. The same standard of informed consent will apply to the treatment extension consent.

Protection against risks The PI is a nephrologist who specializes in bone and mineral disorders and renal osteodystrophy. All personnel involved in the research have passed or will pass the test "Protection of Human Subjects in Research," by the Collaborative Institutional Training Initiative (CITI) at the University of Miami. All investigators and key personnel have received or will receive training for the Health Insurance Portability and Accountability Act (HIPAA) (levels 1 and 2).

Monthly and quarterly monitoring: Monthly telephone or personal contact will be made by the study coordinators to the patients in order to monitor possible adverse events or reactions. Thereafter, every three months, patients will be seen by the study coordinators who will perform a general health assessment. At these monitoring visits, there will be blood draws for monitoring safety. The PI will be available at all times for phone consultation via cell phone and/or a 1-800 telephone number of the University of Kentucky Healthcare written on the consent forms.

Teriparatide for patients with low bone turnover: Patients with increased baseline risk of osteosarcoma will be excluded from this study (Paget's disease of bone, pediatric populations and young adults with open epiphyses, or prior external beam or implant radiation therapy). Our inclusion/exclusion criteria eliminate all of these patients. There are no direct contraindications given for CKD patients given in the package inserts and the safety web page. However, because bone loss with CKD-5D is not specifically addressed in the indications, we have obtained an IND (Investigational New Drug) from the FDA.

If during the monthly monitoring calls/visits or quarterly visits patients complain of new onset adverse reactions such as arthralgia, pain, nausea, dizziness or leg cramps, the patients will be counseled regarding standard treatment measures. Follow-up contact will be made in one week and if symptoms persist, treatment will be discontinued until the next regularly scheduled quarterly monitoring visit. Follow-up communication will occur within 1 week +/- 3 days and if problems persist despite discontinuation, patients will be referred to his/her primary care provider.

If patients complain of injection site reactions, they will be counseled regarding their injection technique and follow-up contact will be made in one week +/- 3 days. If reactions persist, treatment will be discontinued until next regularly scheduled quarterly monitoring visit. If problems persist despite discontinuation, patients will be referred to his/her primary care provider and their participation in the study will end.

In the rare case where PTH level maintenance requires cinacalcet doses that induce serum calcium levels below 8.5 mg/dL, treatment will cease and patients will be excluded from further participation in the study.

Alendronate for patients with normal or high bone turnover: Our inclusion/exclusion criteria cover all of the above-mentioned contra-indications. To be safe, we have obtained an IND from the FDA

If during the monthly monitoring calls/visits or quarterly visits patients complain of new onset gastrointestinal problems, the patients will be counseled regarding the drug intake technique, and standard treatment will be given including over the counter antacids or proton pump inhibitors. Follow-up contact will be made in one week +/- 3 days and if symptoms persist, study treatment will be discontinued until the next regularly scheduled quarterly monitoring visit. If symptoms have disappeared at this visit, treatment will be reinstituted and monitoring will continue. If symptoms respond within 1 week to antacid management, study treatment will be reinstituted. Thereafter, if patients complain of new onset symptoms at the next monthly monitoring call or call themselves earlier, treatment will be discontinued and study participation will end.

If patients complain of new onset musculoskeletal pain, they will be given over-the-counter pain medication and follow-up contact will be made in one week +/- 3 days. If pain persists, study treatment will be discontinued until next regularly scheduled quarterly monitoring visit. Follow-up communication will occur within 1 week +/- 3 days and if problems persist despite discontinuation, patients will be referred to his/her primary care provider.

Blood draws. Compression after blood drawing will reduce the incidence of bruising. All blood draws will be performed with the patient in the sitting position to avoid falls after fainting.

Confidentiality. All patient information will be coded, and the master data kept under lock and key in the study coordinators' office. Access to the codes will be available only to the PI, the data manager/analyst and study coordinators.

Benefit vs. Risk: Describe potential benefits to the subject(s); include potential benefits to society and/or general knowledge to be gained. Describe why the risks to subjects are reasonable in relation to the anticipated benefit(s) to subjects and in relation to the importance of the knowledge that may reasonably be expected to result. If you are using vulnerable subjects (e.g., impaired consent capacity, pregnant women, etc…), justify their inclusion by describing the potential benefits of the research in comparison to the subjects' vulnerability and the risks to them. For information about inclusion of certain vulnerable populations, see the IRB/ORI Standard Operating Procedure for Protection of Vulnerable Subjects [C3.0100] [PDF].

The information gained from this research can directly benefit CKD-5D patients. Reversal of bone loss may result in reduction of bone pain and fracture risk. Moreover, participation in the study and recognition of bone loss may motivate them to adjust their diet and lifestyle and to be more compliant with their therapeutic regimen. The risks of the proposed treatments are well controlled by the careful monitoring protocol. The information gathered from this study will have a direct impact on the clinical management of patients

with CKD-5D at risk for bone loss. The risks from BMD measurements, CAVC measurements and blood draws are small; therefore, the benefits far outweigh the risks.
Based on the knowledge to be gained in the study, we will be able to provide practicing nephrologists with a bone turnover specific individualized treatment regimen for CKD patients with low bone mass. If our treatment regimens prove successful, we will reverse bone loss in these patients thereby reducing fracture risk. There may also be an as yet undetermined retardation of CAVC progression and the associated risk for cardiovascular events in these patients. We will also be able to compare QCT to DXA for measurement of bone mass in these patients and to determine whether DXA, with its lower radiation dose, lower cost and wider availability, can be used in lieu of QCT.

Available Alternative Treatment(s): Describe alternative treatments and procedures that might be advantageous to the subjects, should they choose not to participate in the study. This should include a discussion of the current standard of care treatment(s).

There are currently 3 medications approved for the treatment of osteoporosis; 2 of which are being used in this study. The third medication for osteoporosis is not being used in this patient population of dialysis patients because there have been reports of severe hypocalcemia requiring hospitalization. If the subject chooses not to participate in the study they should continue current standard of care treatment with their primary physician and nephrologist.

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Research Materials, Records and Privacy: Identify the sources of research material obtained from individually identifiable living human subjects. Indicate what information (specimens, records, data, genetic information, etc.) will be recorded and whether use will be made of existing specimens, records or data. Explain why this information is needed to conduct the study.

Return of Research Results or Incidental Findings (if applicable):
If research has the potential to identify individual results or discover incidental findings that could affect the health of a subject, describe plans to assess, manage, and if applicable disclose findings with individual subjects or provide justification for not disclosing. For IRB expectations, refer to the UK IRB “Frequently Asked Questions (FAQs) on the Return of Research Results or Incidental Research Findings" [PDF].

The sources of research material will be the results of BMD measurements by DXA and QCT, MDCT, echocardiogram and bone markers in at specified monitoring visits. These data will be recorded. The following data from medical records will also be recorded: demographic information, personal/medical characteristics, medical history, dialysate calcium concentration levels, duration of hemo- or peritoneal dialysis, primary kidney disease, therapeutic modalities including type and dose of phosphate binder, vitamin D therapy and calcimimetics, and serum calcium, phosphorus, bicarbonate, albumin, and calcidiol. If any incidental findings are reported on the subjects that could have effects on their health we will inform the subject’s nephrologist to perform further evaluation if necessary.

Confidentiality: Specify where the data/specimens will be stored and how the researcher will protect both the data and/or specimens with respect to privacy and confidentiality. Address physical security measures (e.g., locked facility, limited access); data security (e.g., password-protection, data encryption); safeguards to protect identifiable research information (e.g., coding, links, certificate of confidentiality); and procedures employed when sharing material or data, (e.g., honest broker (if applicable), written agreement with recipient not to re-identify). If you plan to procure, store, and/or share material (tissue/specimens/data) expressly for use in current or future research, describe measures that you will take to secure and safeguard confidentiality and privacy.

Describe whether data/specimens will be maintained indefinitely or destroyed. If maintained, specify whether identifiers will be removed from the maintained information/material. If identifiers will not be removed, provide justification for retaining them. If the data/specimens will be destroyed, describe how and when the data/specimens will be destroyed [Note: The investigator is responsible for retaining the signed consent and assent documents and IRB research records for at least six years after study closure as outlined in the Study Closure SOP [PDF]. If the research falls under the authority of FDA or other regulatory agency, the investigator is responsible for retaining the signed documents and IRB records for the period specified if longer than six years after completion of the study]. For multi-site studies, the PI consults the study sponsor regarding retention requirements, but must maintain records for a minimum of six years after study closure. Also, specify who will access the identified data/specimens, and why they need access. If applicable, describe what measures will be taken to ensure that subject identifiers are not given to the investigator. If applicable, describe procedures for sharing data/specimens with entities not affiliated with UK.

> *NIH-funded genomic research*: The National Institutes of Health (NIH) Genomic Data Sharing (GDS) Policy sets forth expectations that ensure the broad and responsible sharing of genomic research data consistent with the informed consent of study participants from which the data was obtained. If you are submitting genomic data to an NIH data repository, describe your NIH data sharing plan.

Please note: The IRB expects researchers to access the minimal amount of identifiers to conduct the study and comply with applicable HIPAA and Family Educational Rights and Privacy Act (FERPA) requirements. If data are going to be collected, transmitted, and/or stored electronically, for appropriate procedures please refer to the guidance document "Confidentiality and Data Security Guidelines for Electronic Data" [PDF].

Also please note that storage of data on cloud services may not be appropriate and is subject to applicable university policies regarding the use of cloud services. If deemed too sensitive or inappropriate to be stored or collected using cloud services, the IRB may require an alternate method of data storage in accordance with applicable university policies and the electronic data security guidance document referenced above.

If a research protocol involves the creation and/or use of a computer program or application, mobile or otherwise, please specify whether the program/application is being developed by a commercial software developer or the research team and provide any relevant information regarding the security and encryption standards used, how data is stored and/or transmitted to the research team, what information about the subjects the program/application will collect, etc. For relevant information to include, see Considerations for Protocol Design Concerning Digital Data [PDF]. The IRB may require software programs created or used for research purposes be examined by a consultant with appropriate Internet technology expertise to ensure subject privacy and data are appropriately protected.

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The identity of all patients will be coded and kept under lock and key with all data. Access to the codes will be available only to the PI, study coordinators, CCTS biostatistician and his research assistant. Data will be collected from several sources, including the study coordinator and PI, for clinical and demographic variables; the CCTS for DXA measurements and results of blood tests; the Gill Heart Institute for bone CT and MDCT results; the image analysis laboratory for QCT. Data forms will be constructed and completed by the study coordinators with input from the project biostatistician. These data will be entered into a REDCap® database. Six years after publication of the results of the study, all electronic files will be erased from computer(s) and all paper files will be shredded.

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Payment: Describe the incentives (e.g., inducements) being offered to subjects for their time during participation in the research study. If monetary compensation is offered, indicate how much the subjects will be paid and describe the terms and schedule of payment. (It is IRB policy that provision should be made for providing partial payment to subjects who withdraw before the completion of the research. Monetary payments should be prorated or paid in full.)

Monetary compensation will be offered to patients for each visit to the UK Chandler Medical Center $150.00 for each scan visit to UK. Travel pay will be reimbursed at the currently approved Mileage Reimbursement Rate. Payment will be made by check after each visit.

Costs to Subjects: Describe any costs for care associated with research (including a breakdown of standard of care procedures versus research procedures), costs of test drugs or devices, and research procedure costs that are the subject's responsibility as a consequence of participating in the research. Describe any offer for reimbursement of costs by the sponsor for research related injury care.

There will be no cost for care associated with the research. The subject's insurance company will be responsible for the costs of all care and treatment during this study that they would normally receive. These are costs that are considered medically reasonable and necessary and would be part of the care received if the subject did not take part in this study.

Data and Safety Monitoring: The IRB requires review and approval of data and safety monitoring plans for greater than minimal risk research, clinical research, or NIH-funded/FDA-regulated clinical investigations.

If you are conducting greater than minimal risk research, clinical research, or your clinical investigation is NIH-funded/FDA-regulated, describe your Data and Safety Monitoring Plan (DSMP). Click here for additional guidance on developing a Data and Safety Monitoring Plan.

If this is a *non-sponsored investigator-initiated* protocol considered greater than minimal risk research, clinical research, or your clinical investigation is FDA-regulated, *and* if you are planning on using a Data and Safety Monitoring Board (DSMB) as part of your DSMP, click here for additional guidance for information to include with your IRB application.

If relying on an independent agent or committee for DSMB services, it is the PI's responsibility to establish the services with the agent or committee. Please be reminded that the PI must submit DSMB reports to the IRB via modification or continuing review.

Written and electronic data recording will be performed by the study coordinators under the supervision of the data manager/analyst Dr. Davenport. Data will be entered by the coordinators into a REDCap® database. All data entry/changes/edits will be performed by the study coordinators only. To assure data quality, quarterly audits will be conducted. The goal is to select 5% of all entered data to be verified for accuracy in 3 ways. The first is data entry errors, which must be maintained at a less than 0.5% error rate to pass inspection; otherwise, a larger sample will be selected on the next audit. The second is to check entries against the patient's medical record. The last is logic checks since the data entered may be correct but not logically related to other data fields. To this end, the data manager/analyst will construct a series of programs to check for outliers and logic errors. All discrepancies must be resolved within two weeks.
Plan for monitoring progress of the trial and protocol compliance.
The PI, co-PI's and study coordinators will monitor and discuss protocol compliance, the rate of recruitment, enrollment, and drop-out rate at weekly meetings. Coordinators will report on results from all patient contacts, including the monthly phone calls or visits and the quarterly treatment monitoring visits.
In addition, the data manager/analyst, (Dr. Davenport) under the direction of the CCTS statistician (Dr. Kryscio) will evaluate the status of accrual, ineligibility, and drop-out rate and perform semiannual sampling and enrollment analyses. The O'Brien-Fleming group sequential boundary will be used to avoid the problems generated by multiple data analyses. Dr. Kryscio will also make decision(s) regarding: (a) superiority (i.e., the hypotheses have been proven); or (b) futility (i.e., continuation of trial will not bring any results). If early termination of the trial is necessary, it will be reported to the IRB, CCTS, FDA and the NIH. The DSMB will also monitor progress, protocol compliance, and adverse events according to the safety monitoring section below.

Safety monitoring
Adverse events (AE's). Adverse events are any untoward medical occurrences associated with the use of study drugs, whether or not considered drug related; this includes adverse reactions (AR's) which are undesirable effects reasonably associated with use of a study drug. The severity of all anticipated (see potential risks listed above) and unanticipated AE's and AR's will be graded according to the National Cancer Institute's Common Toxicity Criteria, version 2.0 (CTC-2) (http://ctep.cancer.gov/reporting/ctc.htmL). Study coordinators (certified physician assistants) will record all adverse events at each encounter with the patient and assign a preliminary severity and attribution grade. The PI will review all adverse events and confirm their grading.
The grades of AE and AR severity will be:
0 = No AE/ARs or within normal limits,
1 = Mild AE/AR
2 = Moderate AE/AR
3 = Severe and undesirable AE/AR
4 = Life-threatening or disabling AE/AR
5 = Death related to AE/AR.
The attribution of the AEs and ARs to the study treatments will be graded as:
1 = Unrelated, AE/AR clearly not related to the investigation
2 = Unlikely, AE/AR doubtfully related to the investigation
3 = Possible, AE/AR may be related to the investigation
4 = Probable, AE/AR likely related to the investigation
5 = Definite, AE/AR clearly related to the investigation.
All AEs and ARs will be recorded in the REDCap® database. The investigator and the study coordinators will review the occurrence of mild to moderate AEs and ARs every 3 months. This file will be accessible upon request to the Data and Safety Monitoring Board. All severe or higher (grade 3-5) AEs and ARs (SAEs and SARs) will be reported to the IRB, the Data and Safety Monitoring Board, and the NIH within 48 hours, according to UK policies, and to the FDA in accordance with IND regulations. All unanticipated AEs and ARs, regardless of attribution, will be reported to the IRB, CCTS, DSMB and the NIH in an expedited manner (48 hours) if they are grade 2 or higher in severity.

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Subject Complaints: Describe procedures (other than information provided in consent document) for handling subject complaints or requests for information about the research. The procedures should offer a safe, confidential, and reliable channel for current, prospective, or past research subjects (or their designated representative) permitting them to discuss problems, concerns and questions, or obtain information.

After enrollment subjects will be given phone numbers, and emails of the research subject advocate of the CCTS, Office of Research Integrity and the University Program for Bioethics and Patients' Rights.

Does your research involve **Non-English Speaking Subjects or Subjects from a Foreign Culture**?

○ Yes ◉ No

Non-English Speaking Subjects or Subjects from a Foreign Culture

Describe how information about the study will be communicated to potential subjects appropriate for their culture, and if necessary, how new information about the research may be relayed to subjects during the study.

Include contact information for someone who can act as a cultural consultant for your study. The person should be familiar with the culture of the subject population and/or be able to verify that translated documents are the equivalent of the English version of documents submitted. The consultant should not have any direct involvement with the study. If you do not know someone who would be willing to act as your cultural consultant, the Office of Research Integrity will try to find someone to fill this role (this may delay the approval process for your protocol). Please include the name, address, telephone number, and email of the person who will act as the cultural consultant for your study. For more details, see the IRB Application Instructions on Research Involving Non-English Speaking Subjects or Subjects from a Foreign Culture.

For recruitment of Non-English speaking subjects, the consent document needs to be in the subject's native language. Download the informed consent template available in the E-IRB "Informed Consent/Assent Process" section and use it as a guide for developing the consent document. (Note: Your translated consent document can be attached to your application in the "Informed Consent" section; **be sure to save your responses in this section first**.)

If research is to be conducted at an international location, identify local regulations, laws, or ethics review requirements for human subject protection. If the project has been or will be reviewed by a local Ethics Committee, attach a copy of the review to the UK IRB using the attachment button below. You may also consult the current edition of the International Compilation of Human Research Standards

Does your study involve **HIV/AIDS research and/or screening for other reportable diseases (e.g., Hepatitis C, etc…)**?

○ Yes ◉ No

HIV/AIDS Research

If you have questions about what constitutes a reportable disease and/or condition in the state of Kentucky, see ORI's summary sheet: "Reporting Requirements for Diseases and Conditions in Kentucky" [PDF].

HIV/AIDS Research: There are additional IRB requirements for designing and implementing the research and for obtaining informed consent. Describe additional safeguards to minimize risk to subjects in the space provided below.

For additional information, visit the online IRB Survival Handbook to download a copy of the "Medical IRB's requirements for Protection of Human Subjects in Research Involving HIV Testing" [D65.0000] [PDF], and visit the Office for Human Research Protections web site for statements on AIDS research, or contact the Office of Research Integrity at 859-257-9428.

PI-Sponsored FDA-Regulated Research

Is this an investigator-initiated study that:

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1) involves testing a Nonsignificant Risk (NSR) Device, or
2) is being conducted under an investigator-held Investigational New Drug (IND) or Investigational Device Exemption (IDE)?

○ Yes ◉ No

PI-Sponsored FDA-Regulated Research

If the answer above is yes, then the PI assumes the regulatory responsibilities of both the investigator and sponsor. The Office of Research Integrity provides a summary list of sponsor IND regulatory requirements for drug trials [PDF], IDE regulatory requirements for SR device trials [PDF], and abbreviated regulatory requirements for NSR device trials [PDF]. For detailed descriptions see FDA Responsibilities for Device Study Sponsors or FDA Responsibilities for IND Drug Study Sponsor-Investigators.

- Describe your (the PI's) experience/knowledge/training (if any) in serving as a sponsor (e.g., previously held an IND/IDE); and
- Indicate if you have transferred any sponsor obligations to a commercial sponsor, contract research organization (CRO), contract monitor, or other entity (provide details or attach FDA 1571).

IRB policy requires mandatory training for all investigators who are also FDA-regulated sponsors (see Sponsor-Investigator FAQs). A sponsor-investigator must complete the applicable Office of Research Integrity web based training, (drug or device) before final IRB approval is granted.

Has the PI completed the mandatory PI-sponsor training prior to this submission?

○ Yes ○ No

If you (the PI) have completed equivalent sponsor-investigator training, you may submit documentation of the content for the IRB's consideration.

Attachments

HIPAA

Is HIPAA applicable? ◉ Yes ○ No

(Visit ORI's Health Insurance Portability and Accountability Act (HIPAA) web page to determine if your research falls under the HIPAA Privacy Regulation.)

If yes, check below all that apply and attach the applicable document(s):

- ☑ HIPAA De-identification Certification Form
- ☐ HIPAA Waiver of Authorization

Attachments

STUDY DRUG INFORMATION

◉ Yes ○ No

If yes, complete the questions below. Additional study drug guidance.

LIST EACH DRUG INVOLVED IN STUDY IN THE SPACE BELOW

Drug Name:

Alendronate, Forteo and Sensipar

Note: Inpatient studies are required by Hospital Policy to utilize the Investigational Drug Service (IDS). Use of IDS is highly recommended, but optional for outpatient studies. Outpatient studies not using IDS services are subject to periodic inspection by the IDS for compliance with drug accountability good clinical practices.

Indicate where study drug(s) will be housed and managed:

☑ Investigational Drug Service (IDS) UK Hospital

Other Location:

Is the study being conducted under a valid Investigational New Drug (IND) application?

◉ Yes ○ No

If Yes, list IND #(s) and complete the following:

122616

IND Submitted/Held by:

Sponsor: ☐		Held By:	
Investigator: ☑		Held By:	Hartmut Malluche, MD
Other: ☐		Held By:	

☐ Checkmark this if the study is being conducted under FDA's Expanded Access Program (e.g., Treatment IND).

- FDA's Expanded Access Program Information (e.g., treatment IND)
- Guidance and definitions: "Expanded Access SOP" (PDF).

Please also complete and attach the Study Drug Form (PDF) (required):

Attachments

Attach Type	File Name
StudyDrug	Study Drug Attachment Alendronate.pdf
StudyDrug	Study Drug Attachment Forteo.pdf
StudyDrug	Study Drug Attachment Sensipar.pdf
StudyDrug	alendronate prescribing info.pdf
StudyDrug	Forteo prescribing information.pdf
StudyDrug	Sensipar prescribing information.pdf
StudyDrug	FDA correspondence for IND.pdf

STUDY DEVICE INFORMATION

A DEVICE may be a:

- component, part, accessory;
- assay, reagent, or in-vitro diagnostic device;
- software, digital health, or mobile medical app;
- other instrument if intended to affect the structure or function of the body, diagnose, cure, mitigate, treat or prevent disease; or
- a homemade device developed by an investigator or other non-commercial entity and not approved for marketing by FDA.

For additional information, helpful resources, and definitions, see ORI's Use of Any Device Being Tested in Research web page.

Does this protocol involve testing (collecting safety or efficacy data) of a medical device including an FDA approved device, unapproved use of an approved device, humanitarian use device, and/or an investigational device?

○ Yes ◉ No

[Note: If a marketed device(s) is only being used to elicit or measure a physiologic response or clinical outcome, AND, NO data will be collected on or about the device itself, you may answer “no” above, save and exit this section, (Examples: a chemo drug study uses an MRI to measure tumor growth but does NOT assess how effective the MRI is at making the measurement; an exercise study uses a heart monitor to measure athletic performance but no safety or efficacy information will be collected about the device itself, nor will the data collected be used for comparative purposes against any other similar device).]

If you answered yes above, please complete the following questions.

LIST EACH DEVICE BEING TESTED IN STUDY IN THE SPACE BELOW

Device Name:

Is the study being conducted under a valid Investigational Device Exemption (IDE) or Humanitarian Device Exemption (HDE) application? See UK HUD SOP (PDF) for guidance.

○ Yes ○ No

If Yes, list IDE or HDE #(s) and complete the following:

IDE/HDE Submitted/Held by:

Sponsor: ☐ Held By:

Investigator: ☐ Held By:

Other: ☐ Held By:

☐ Check if this is a Treatment or Compassionate Use IDE under the Food and Drug Administration (FDA) Early Expanded Access program.

- FDA's Early Expanded Access Program Information
- Guidance and definitions: "Medical Device Clinical Investigations, Compassionate Use, and Treatment IDE SOP" (PDF)

Does the intended use of any device used in this study meet the regulatory definition of Significant Risk (SR) device?

○ Yes. Device(s) as used in this study presents a potential for serious risk to the health, safety, or welfare of a subject and (1) is intended as an implant; or (2) is used in supporting or sustaining human life; or (3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or (4) otherwise presents a potential

for serious risk to the health, safety, or welfare of a subject.

No. All devices, as used in this study do not present a potential for serious risk to the health, safety, or welfare of subjects/participants.

Please also complete and attach the Study Device Form (PDF) (required):

Attachments

RESEARCH SITES

In order for this section to be considered complete, you must click "SAVE" after ensuring all responses are accurate.

A) Check all the applicable sites listed below at which the research will be conducted. If none apply, you do not need to check any boxes.

UK Sites

- ☐ UK Classroom(s)/Lab(s)
- ☐ UK Clinics in Lexington
- ☐ UK Clinics outside of Lexington
- ☐ UK Healthcare Good Samaritan Hospital
- ☑ UK Hospital

Schools/Education Institutions

- ☐ Fayette Co. School Systems *
- ☐ Other State/Regional School Systems
- ☐ Institutions of Higher Education (other than UK)

***Fayette Co. School systems, as well as other non-UK sites, have additional requirements that must be addressed. See ORI's IRB Application Instructions - Off-site Research web page for details.**

Other Medical Facilities

- ☐ Bluegrass Regional Mental Health Retardation Board
- ☐ Cardinal Hill Hospital
- ☐ Eastern State Hospital
- ☐ Norton Healthcare
- ☐ Nursing Homes
- ☐ Shriner's Children's Hospital
- ☐ Veterans Affairs Medical Center
- ☐ Other Hospitals and Med. Centers

- ☐ Correctional Facilities
- ☐ Home Health Agencies
- ☐ International Sites

List all other non-UK owned/operated locations where the research will be conducted:*

*A letter of support and local context is required from non-UK sites. See *Letters of Support and Local Context* on the IRB Application Instructions - Off-Site Research web page for more information.

dialysis units

Attachments

Attach Type	File Name
-Individual Investigator Agreement	Potential Davita Dialysis Units update 3.29.18.docx
-Individual Investigator Agreement	Master list of Off-site Dialysis units 2019 highlighted.pdf
-Individual Investigator Agreement	Master list of Off-site Dialysis units 2019 clean.pdf
-Individual Investigator Agreement	Charles Shelton IIA.pdf
-IRB Approval (non-UK)	DCI AOR 06.18.2018.pdf

-IRB Approval (non-UK)	Clinical Trial Agreement FMC.pdf
-IRB Approval (non-UK)	Davita Study Approval Terms.pdf
-IRB Approval (non-UK)	DCI ARO.pdf
-IRB Approval (non-UK)	ARA.UKRF Signed clinical trial agreement.pdf
-Letter of Support & Local Context	DCI Eastgate signature page signed.pdf

B) Is this a multi-site study for which you are the lead investigator or UK is the lead site? ○ Yes ◉ No

If **YES**, you must describe the plan for the management of reporting unanticipated problems, noncompliance, and submission of protocol modifications and interim results from the non-UK sites in the E-IRB "Research Description" section under *Resources*.

If the non-UK sites or non-UK personnel are *engaged* in the research, there are additional federal and university requirements which need to be completed for their participation, such as the establishment of a cooperative IRB review agreement with the non-UK site. Questions about the participation of non-UK sites/personnel should be discussed with the ORI staff at (859) 257-9428.

RESEARCH ATTRIBUTES

Indicate the items below that apply to your research. Depending on the items applicable to your research, you may be required to complete additional forms or meet additional requirements. Contact the ORI (859-257-9428) if you have questions about additional requirements.

☐ Not applicable

Check All That Apply

	Click applicable listing(s) for additional requirements and/or information:
☐ Academic Degree/Required Research	• Cancer Research (MCC PRMC)
☐ Aging Research	• Certificate of Confidentiality (look up "Confidentiality/Privacy...")
☐ Alcohol Abuse Research	• CCTS (Center for Clinical and Translational Science)
☐ Cancer Research	• Clinical Research (look up "What is the definition of....)
☐ Certificate of Confidentiality	• Clinical Trial (look up "What is the definition of....)
☑ CCTS-Center for Clinical & Translational Science	Determine if research meets NIH definition of clinical trial; *Reminder: Ensure compliance with clinicaltrials.gov registration requirements for applicable clinical trials and Good Clinical Practice (GCP) training requirements.
☑ Clinical Research	
☐ Clinical Trial	
☐ Clinical Trial Multicenter(excluding NIH Cooperative Groups)	• Collection of Biological Specimens for Banking (look up "Specimen/Tissue Collection...")
☐ Clinical Trial NIH cooperative groups (i.e., SWOG, RTOG)	• Collection of Biological Specimens (look up "Specimen/Tissue Collection...")
☐ Clinical Trial Placebo Controlled Trial	• Community-Based Participatory Research (look up "Community-Engaged...")
☐ Clinical Trial UK Only	• Data & Safety Monitoring Board (DSMB)
☐ Collection of Biological Specimens	*For Medical IRB: Service Request Form for CCTS DSMB
☐ Collection of Biological Specimens for Banking	
☐ Community-Based Participatory Research	• Data & Safety Monitoring Plan
☑ Data & Safety Monitoring Board	• Deception*
☐ Data & Safety Monitoring Plan	*For deception research, also go to the E-IRB Application Informed Consent section, checkmark and complete "Request for Waiver of Informed Consent Process"
☐ Deception	
☐ Drug/Substance Abuse Research	• Emergency Use (Single Patient) [attach Emergency Use Checklist] (PDF)
☐ Educational/Student Records (e.g., GPA, test scores)	• Genetic Research (look up "Specimen/Tissue Collection...")
☐ Emergency Use (Single Patient)	• Gene Transfer
☐ Genetic Research	• HIV/AIDS Research (look up "Reportable Diseases/Conditions")
☐ Gene Transfer	• Screening for Reportable Diseases [E2.0000] (PDF)
☐ GWAS (Genome-Wide Association Study) or NIH-funded study generating large scale genomic data	• International Research (look up "International & Non-English Speaking")
☐ International Research	• NIH Genomic Data Sharing (GDS) Policy (PDF)
☐ Internet Research	• Planned Emergency Research Involving Waiver of Informed Consent*
☐ Planned Emergency Research Involving Waiver of Informed Consent	*For Planned Emergency Research Involving Waiver of Informed Consent, also go to the E-IRB Application Informed Consent section, checkmark and complete "Request for Waiver of Informed Consent Process"
☐ Pluripotent Stem Cell Research	
☐ Recombinant DNA	• Use of radioactive material, ionizing radiation or
☐ Survey Research	
☐ Transplants	
☐ Use of radioactive material, ionizing radiation, or x-rays [Radiation Safety Committee review required]	
☐ Vaccine Trials	

x-rays for research

FUNDING/SUPPORT

If the research is being submitted to, supported by, or conducted in cooperation with an external or internal agency or funding program, indicate below all the categories that apply.

☐ Not applicable

Check All That Apply

- ☐ Grant application pending
- ☑ (HHS) Dept. of Health & Human Services
  - ☑ (NIH) National Institutes of Health
  - ☐ (CDC) Centers for Disease Control & Prevention
  - ☐ (HRSA) Health Resources and Services Administration
  - ☐ (SAMHSA) Substance Abuse and Mental Health Services Administration
- ☐ (DoJ) Department of Justice or Bureau of Prisons
- ☐ (DoE) Department of Energy
- ☐ (EPA) Environmental Protection Agency
- ☐ Federal Agencies Other Than Those Listed Here
- ☐ Industry (Other than Pharmaceutical Companies)
- ☐ Internal Grant Program w/ proposal
- ☐ Internal Grant Program w/o proposal
- ☐ National Science Foundation
- ☐ Other Institutions of Higher Education
- ☐ Pharmaceutical Company
- ☐ Private Foundation/Association
- ☐ U.S. Department of Education
- ☐ State

Other:

Click applicable listing(s) for additional requirements and/or information:

- (HHS) Dept. of Health & Human Services
- (NIH) National Institutes of Health
- (CDC) Centers for Disease Control & Prevention
- (HRSA) Health Resources & Services Administration
- (SAMHSA) Substance Abuse & Mental Health Services Administration
- Industry (Other than Pharmaceutical Companies) [IRB Fee Info]
- National Science Foundation
- (DoEd) U.S. Department of Education
- (DoJ) Department of Justice or Bureau of Prisons
- (DoE) Department of Energy Summary and Department of Energy Identifiable Information Compliance Checklist
- (EPA) Environmental Protection Agency

Specify the funding source and/or cooperating organization(s) (e.g., National Cancer Institute, Ford Foundation, Eli Lilly & Company, South Western Oncology Group, Bureau of Prisons, etc.):

NIH

Add Related Grants

If applicable, please search for and select the OSPA Account number or Electronic Internal Approval Form (eIAF) # (notif #) associated with this IRB application using the "Add Related Grants" button.
If required by your funding agency, upload your grant using the "Grant/Contract Attachments" button.

Add Related Grants

Grant/Contract Attachments

The research involves use of Department of Defense (DoD) funding, military personnel, DoD facilities, or other DoD resources.

(See DoD SOP [PDF] and DoD Summary [PDF] for details)

○ Yes ◉ No

Using the “attachments” button (below), attach applicable materials addressing the specific processes described in the DoD SOP.

DOD SOP Attachments

Additional Certification: (If your project is federally funded, your funding agency may request an Assurance/ Certification/Declaration of Exemption form.) Check the following if needed:

☐ Protection of Human Subjects Assurance/Certification/Declaration of Exemption (Formerly Optional Form – 310)

OTHER REVIEW COMMITTEES

If you check any of the below committees, additional materials may be required with your application submission.

Does your research fall under the purview of any of the other review committees listed below? [*If yes, check all that apply and attach applicable materials using the attachment button at the bottom of your screen.*]

◉ Yes ○ No

☐ Institutional Biosafety Committee
☑ Radiation Safety Committee
☐ Radioactive Drug Research Committee
☐ Markey Cancer Center (MCC) Protocol Review and Monitoring Committee (PRMC)
☐ Graduate Medical Education Committee (GME)
☐ Office of Medical Education (OME)

Additional Information

- Institutional Biosafety Committee (IBC)--Attach required IBC materials
- Radiation Safety Committee (RSC)-- For applicability, see instructions and/or upload form [WORD] [PDF]
- Radioactive Drug Research Committee (RDRC)--information
- Markey Cancer Center (MCC) Protocol Review and Monitoring Committee (PRMC)**--Attach MCC PRMC materials, if any, per instructions
- See requirement of Office of Medical Education (OME)
- See requirement of Graduate Medical Education Committee (GME)

Attachments

**** If you are proposing a study involving cancer research, be sure to have "Cancer Research" marked in the E-IRB "Research Attributes" section.** If your study involves cancer research, ORI will provide a copy of your research protocol to the Markey Cancer Center (MCC) Protocol Review and Monitoring Committee (PRMC). The MCC PRMC is responsible for determining whether the study meets the National Cancer Institute (NCI) definition of a clinical trial and for issuing documentation to you (the investigator) which confirms either that PRMC approval has been obtained or that PRC review is not required. Your IRB application will be processed and reviewed independently from the PRMC review.

ADDITIONAL INFORMATION/MATERIALS

Do you want specific information inserted into your approval letter? ◉ Yes ○ No

Approval Letter Details (e.g., serial #):

Submission Description: If you wish to have specific details included in your approval letter (e.g., serial #, internal tracking identifier, etc…), type in the box below exactly what you wish to see on the approval letter. What you type will automatically appear at the top of all approval letters, identical to how you typed it, until it is changed by you (Hint: don't include instructions or questions to ORI staff as those will appear in your approval letter). **If these details need to be changed as a result of revisions, continuation review, or modifications to the application, you are responsible for updating the content of the field below accordingly.**

Serial #69

Protocol/Product Attachments - For each item checked, please attach the corresponding material.

- ☐ Detailed protocol
- ☐ Dept. of Health & Human Services (DHHS) approved protocol (such as NIH sponsored Cooperative Group Clinical Trial)
- ☐ Drug Documentation (e.g., Investigator Brochure; approved labeling; publication; FDA correspondence, etc.)
- ☐ Device Documentation (e.g., Manufacturer information; patient information packet; approved labeling; FDA correspondence, etc.)
- ☐ Other Documents

Protocol/Product Attachments

NOTE: Instructions for Dept. of Health & Human Services (DHHS)-approved protocol]

If you have password protected documents, that feature should be disabled prior to uploading to ensure access for IRB review.

Additional Materials:

If you have other materials you would like to include in your application for the IRB's consideration, please attach using the Attachments button below.

[To view what materials are currently attached to your application, go to "Application Links" in the menu bar on the left and click "All Attachments".]

Attachments

Attach Type	File Name
AdditionInfoConsiderations	Withdrawal Log October 2019 .pdf
AdditionInfoConsiderations	Adverse Event Log October 2019.pdf

SIGNATURES (ASSURANCES)

On all IRB applications there is a requirement for additional assurances by a Department Chairperson (or equivalent) [hereafter referred to as "Department Authorization" (DA)], and when applicable, a Faculty Advisor (FA) (or equivalent), which signifies the acceptance of certain responsibilities and that the science is meritorious and deserving of conduct in humans. Note: the individual assigned as DA *should not* also be listed in the Study Personnel section, the individual assigned as FA *should* be listed in the Study Personnel section.

For a list of responsibilities reflected by signing the Assurance Statement, download the guidance document "What does the Department Chairperson's Assurance Statement on the IRB application mean?"

Required Signatures:

First Name	Last Name	Role	Department	Date Signed	
Hartmut	Malluche	Principal Investigator	Internal Medicine	12/13/2017 10:01 AM	View/Sign
David	Moliterno	Department Authorization	Internal Medicine	03/30/2018 10:37 AM	View/Sign

Principal Investigator's Assurance Statement

I understand the University of Kentucky's policies concerning research involving human subjects and I agree:

1. To comply with all IRB policies, decisions, conditions, and requirements;
2. To accept responsibility for the scientific and ethical conduct of this research study;
3. To obtain prior approval from the Institutional Review Board before amending or altering the research protocol or implementing changes in the approved consent/assent form;
4. To report to the IRB in accord with IRB/IBC policy, any adverse event(s) and/or unanticipated problem(s) involving risks to subjects;
5. To complete, on request by the IRB for Full and Expedited studies, the Continuation/Final Review Forms;
6. To notify the Office of Sponsored Projects Administration (OSPA) and/or the IRB (when applicable) of the development of any financial interest not already disclosed;
7. Each individual listed as study personnel in this application has received the mandatory human research protections education (e.g., CITI);
8. Each individual listed as study personnel in this application possesses the necessary experience for conducting research activities in the role described for this research study.
9. To recognize and accept additional regulatory responsibilities if serving as both a sponsor and investigator for FDA regulated research.

☑ Furthermore, by checking this box, I also attest that:

- I have appropriate facilities and resources for conducting the study;
- I am aware of and take full responsibility for the accuracy of all materials submitted to the IRB for review;
- If applying for an exemption, I also certify that the only involvement of human subjects in this research study will be in the categories specified in the Protocol Type: Exemption Categories section.
- If applying for an Abbreviated Application (AA) to rely on an external IRB, I understand that certain items above (1, 3, 4, 7-8) may not apply, or may be altered due to external institutional/IRB policies. I document my agreement with the Principal Investigator Reliance Assurance Statement by digitally signing this application.

*You will be able to "sign" your assurance after you have sent your application for signatures (use Submission section). Please notify the personnel required for signing your IRB application after sending for signatures. Once all signatures have been recorded, you will need to return to this section to submit your application to ORI.

Department Authorization

☑ This is to certify that I have reviewed this research protocol and that I attest to the scientific validity and importance of this study; to the qualifications of the investigator(s) to conduct the project and their time available for the project; that

facilities, equipment, and personnel are adequate to conduct the research; and that continued guidance will be provided as appropriate. When the principal investigator assumes a sponsor function, the investigator has been notified of the additional regulatory requirements of the sponsor and by signing the principal investigator Assurance Statement, confirms he/she can comply with them.

*If the Principal Investigator is also the Chairperson of the department, the Vice Chairperson or equivalent should complete the "Department Authorization".

**IF APPLICABLE FOR RELIANCE: I attest that the principal investigator has been notified of the regulatory requirements of both the Reviewing and Relying IRBs, according to the information provided in the E-IRB application. The attached Reliance Assurance Statement, signed by the principal investigator, confirms that he/she can comply with both sets of IRB requirements.

SUBMISSION INFORMATION

Each Section/Subsection in the menu on the left must have a checkmark beside it (except this Submission section) indicating the Section/Subsection has been completed; otherwise your submission for IRB review and approval will not be able to be sent to the Office of Research Integrity/IRB.

Please remember to update, when applicable, the Approval Letter Details text box under the Additional Information section to ensure verbiage you want on your approval letter is accurate.

If your materials require review at a convened IRB meeting which you will be asked to attend, it will be scheduled on the next available agenda and a message will be forthcoming to notify you of the date.

If you are making a change to an attachment, you need to delete the attachment, upload a highlighted version that contains the changes (use Document Type of "Highlighted Changes"), and a version that contains the changes without any highlights (use the appropriate Document Type for the item(s)). Do **not** delete approved attachments that are still in use.

Modification Request Information

Select One:

- (•) This modification does not increase risk to study participants.
- ( ) This modification may or will increase risk to study participants.

Is this modification request due to an Unanticipated Problem/Adverse Event, or Protocol Violation?

( ) Yes (•) No

In your professional opinion, does this modification involve information that might relate to a subject's willingness to continue to take part in the research?

( ) Yes (•) No

If yes, state how the information will be communicated to subjects (i.e., re-consent, send letter, etc.):

For each proposed modification, include a justification.

Example: Jane Doe, MD, is being added as co-investigator because she has expertise with the subjects on this protocol. She has completed human subject protections training, and is authorized to obtain consent.

formatting update, informed consent

Your protocol has been submitted.

	Document Type	File Loaded	Document Description	File Size	Modified By	Mod Date
	Stamped Consent Form	Screening consent CLEAN 8.26.2019.pdf		0.229	jato226	2/12/2020 4:06:48 PM
	Stamped Consent Form	clean Extended Treatment Consent 9.3.2019 pdf.pdf		0.256	jato226	2/12/2020 4:06:48 PM
	Stamped Consent Form	treatment consent 1.30.20 clean.pdf		0.379	jato226	2/12/2020 4:06:48 PM
	ApprovalLetter	ApprovalLetter.pdf		0.058	jato226	2/12/2020 4:06:48 PM
	Informed ConsentHIPAA Combined Form	treatment consent 1.30.20 clean.pdf	Treatment Consent, CLEAN	0.455	jato226	2/12/2020 2:40:47 PM
	AdditionInfoConsiderations	Adverse Event Log October 2019.pdf	Adverse Event Log 2019	0.442	kmde222	10/18/2019 8:34:09 AM
	AdditionInfoConsiderations	Withdrawal Log October 2019 .pdf	withdrawal log 2019	0.159	kmde222	10/18/2019 8:33:07 AM
	Informed ConsentHIPAA Combined Form	clean Extended Treatment Consent 9.3.2019 pdf.pdf	Extended consent CLEAN	0.269	kmde222	9/3/2019 9:57:03 AM
	Informed ConsentHIPAA Combined Form	Screening consent CLEAN 8.26.2019.pdf	Screening Consent CLEAN 8.26.2019	0.232	jato226	8/29/2019 9:57:42 AM
	ResearchProcedures	figure 3 7.22.2019 pdf.pdf	ResearchProcedures	0.092	kmde222	8/14/2019 8:27:40 AM
	StudyDesign	Form B graph 8.8.2019.pdf		0.044	kmde222	8/14/2019 6:59:31 AM
	-Individual Investigator Agreement	Charles Shelton IIA.pdf	IIA Shelton	0.541	jato226	4/30/2019 8:14:13 AM
	-IRB Approval (non-UK)	DCI AOR 06.18.2018.pdf	DCI ARO	0.055	kmde222	11/9/2018 8:49:26 AM
	-Individual Investigator Agreement	Master list of Off-site Dialysis units 2019 clean.pdf	Master list of off-site units clean	0.075	kmde222	11/8/2018 12:07:42 PM
	-Individual Investigator Agreement	Master list of Off-site Dialysis units 2019 highlighted.pdf	Master list of off-site units highlighted	0.078	kmde222	11/8/2018 12:07:17 PM
	-Letter of Support & Local Context	DCI Eastgate signature page signed.pdf	DCI Signature Page	0.063	tmpa228	4/30/2018 12:27:36 PM
	-Individual Investigator Agreement	Potential Davita Dialysis Units update 3.29.18.docx		0.030	nkhugh1	3/29/2018 10:13:31 AM
	-IRB Approval (non-UK)	ARA.UKRF Signed clinical trial agreement.pdf		0.482	nkhugh1	12/12/2017 10:20:28 AM
	-IRB Approval (non-UK)	DCI ARO.pdf		0.239	nkhugh1	12/11/2017 10:55:06 AM
	-IRB Approval (non-UK)	Davita Study Approval Terms.pdf		0.307	nkhugh1	12/11/2017 10:55:00 AM
	-IRB Approval (non-UK)	Clinical Trial Agreement FMC.pdf		0.188	nkhugh1	12/11/2017 10:54:48 AM
	StudyDrug	FDA correspondence for IND.pdf	FDA correspondence letter for IND	0.120	nkhugh1	12/11/2017 10:01:35 AM
	StudyDrug	Sensipar prescribing information.pdf	Sensipar Prescribing Information	0.272	nkhugh1	12/11/2017 10:01:13 AM
	StudyDrug	Forteo prescribing information.pdf	Forteo prescribing information	0.152	nkhugh1	12/11/2017 10:00:43 AM
	StudyDrug	alendronate prescribing info.pdf	Alendronate prescribing information	0.654	nkhugh1	12/11/2017 10:00:20 AM
	StudyDrug	Study Drug Attachment Sensipar.pdf	Sensipar Study Drug Form	0.296	nkhugh1	12/11/2017 9:59:58 AM
	StudyDrug	Study Drug Attachment Forteo.pdf	Forteo Study Drug Form	0.295	nkhugh1	12/11/2017 9:59:38 AM
	StudyDrug	Study Drug Attachment Alendronate.pdf	Alendronate Study Drug Form	0.295	nkhugh1	12/11/2017 9:59:14 AM

Protocol Changes

Protocol Number: 43175

Additional Information/Materials AdditionalInformation changed by jato226 on 2/12/2020 2:46:31 PM

Serial #6~~7~~9

Study Personnel Changes:

No Changes

There are no recorded changes to study personnel.

Study Personnel Comment by Jacqueline Williams - ORI to IRB/PI on 2/12/2020 11:07:08 AM

Our records indicate Nedda Hughes, listed on the research protocol, has not completed continuing human subject's protection (HSP) training as mandated by University of Kentucky.

Additional Information/Materials Comment by Jacqueline Williams - ORI to IRB/PI on 2/12/2020 2:47:42 PM

Approval Letter Details (e.g., serial #) subsection of the Additional Information/Materials section was updated by request of PI staff to Serial 69.

Additional Information/Materials Comment by Jacqueline Williams - ORI to PI on 2/12/2020 11:25:50 AM

Please verify that the information in the Approval Letter Details (e.g., serial #) subsection of the Additional Information/Materials section is correct for this modification request.

Informed Consent Comment by Katelyn Hellman - PI to PI on 2/12/2020 12:09:11 PM

Please see the IRB stamp has been removed and the tracked changes also has been uploaded.

Informed Consent Comment by Jacqueline Williams - ORI to PI on 2/12/2020 11:23:41 AM

Please provide a tracked changes version of the Treatment consent showing changes made to the previously approved version to the current proposed version.

Informed Consent Comment by Jacqueline Williams - ORI to PI on 2/12/2020 11:22:08 AM

Please remove the IRB stamp in the upper right hand corner of pages 2 through 13 from the CLEAN version of the Treatment Consent provided

Combined Consent and Authorization to Participate in a Research Study

Renal Osteodystrophy: An Individual Management Approach

Treatment Consent

WHY ARE YOU BEING INVITED TO TAKE PART IN THIS RESEARCH?

You are being invited to take part in a research study about the treatment of bone loss (osteoporosis or osteopenia) in patients on dialysis. You are being invited to take part in this research study because you have kidney disease, are currently on dialysis and a screening Dual-energy X-ray Absorptiometry (DXA) bone density scan indicated that you have loss of bone density. If you volunteer to take part in this study, you will be one of about 120 people to do so at the University of Kentucky.

WHO IS DOING THE STUDY?

The person in charge of this study is Hartmut Malluche, MD of University of Kentucky, Department of Internal Medicine, Division of Nephrology, Bone and Mineral Metabolism. There may be other people on the research team assisting at different times during the study.

WHAT IS THE PURPOSE OF THIS STUDY?

The purpose of this study is to determine if an individualized treatment regimen based on bone turnover for patients with bone loss and on dialysis will reverse bone loss and slow down the progression of calcium deposits in the vessels of the heart.

ARE THERE REASONS WHY YOU SHOULD NOT TAKE PART IN THIS STUDY?

The reasons for you to be excluded from volunteering for this study are:

- Pregnant, or trying to become pregnant or are breastfeeding.
- Less than 21 year of age
- Scheduled for a kidney transplant
- Have a history of alcohol or drug dependence
- Have not been on dialysis for at least 3 months
- Abnormal serum calcium
- Systemic illnesses or organ diseases that may affect bone (except type 1 or type 2 diabetesmellitus)
- Clinical condition that may limit study participation (e.g., unstable angina, respiratory distress, infections)
- Known Paget ’s disease of bone
- Prior external beam or implant radiation therapy involving the skeleton only if randomized toteriparatide treatment
- Planning to move out of the area within 2 year of the study

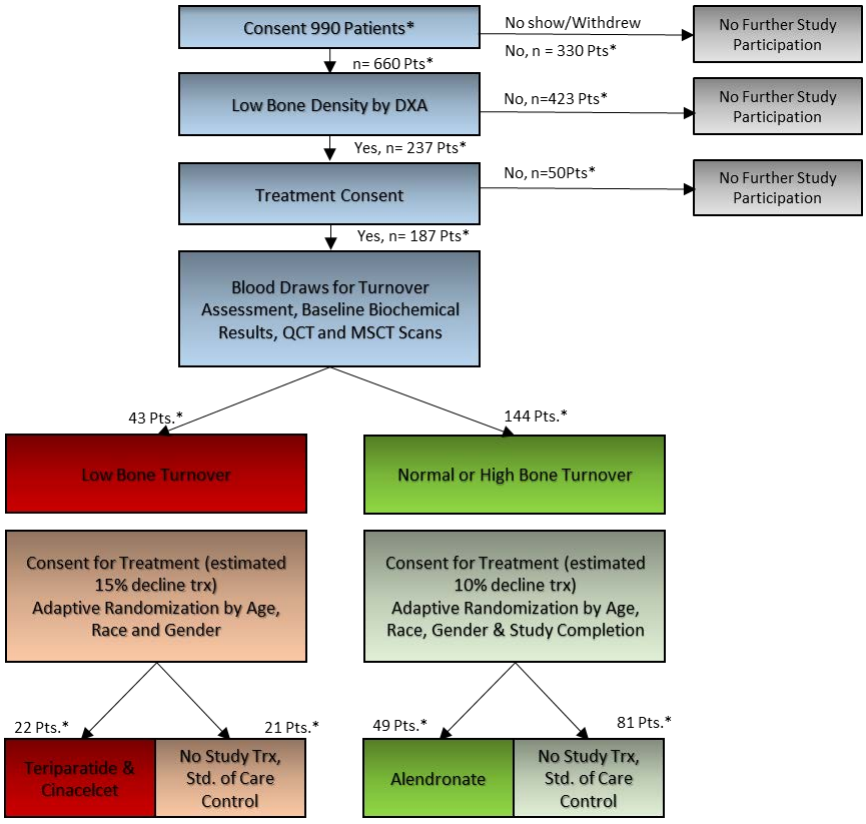
- Bone Mineral Density (BMD) t-score of the radius less than -3.5 by DXA during the screening phase only if randomized to teriparatide treatment
- Current treatment with medicines containing digoxin.
- Planned or anticipated oral surgery within the next 24 months
- Inability to stand or sit upright for at least 30 minutes
- Abnormalities of the esophagus which delay esophageal emptying such as stricture (narrowing) or archalasia (a condition that prevents normal swallowing).
- Vitamin D (Calcidiol) level below the normal range

WHERE IS THE STUDY GOING TO TAKE PLACE AND HOW LONG WILL IT LAST?

The research procedures will be conducted at the UK Medical Center. You will have a visit in your dialysiscenter or you may need to come to the Center for Clinical and Translational Science (CCTS), 5th floor, close to elevator C up to 8 times during this part of the study. You will also visit the Gill Imaging Center at the Gill Heart Center and the Comprehensive Breast Care Center at Markey Cancer Center 4 times during the study. A map will be given to you and research personnel will assist you. This study will involve approximately 12-16 hours of your time over the course of 2 years and a follow up phone call 3 months after finishing two years of treatment.

WHAT WILL YOU BE ASKED TO DO?

Study Protocol; *All patient numbers are estimates based on enrollment to date.



If you were found to have low bone density by DXA scan and agree to participate in this treatment study, you will have blood drawn for bone turnover assessment to determine which study arm you may be a candidate for. Once it is determined if you are in the low bone turnover arm or the normal or high bone turnover arm (See Figure Above) you will then be randomized to either a treatment arm or a control arm that does not receive any treatment. Half of the patients in the low turnover group will receive active therapy and half will receive standard of care (no study treatment) while one quarter of the patients in the high turnover group will receive active therapy and three quarters will receive standard of care (no study treatment).

Low Bone Turnover Arm:

Patients in the low bone turnover arm who are receiving the study medication will be taking teriparatide once a day. This medication is administered by an injection under the skin from a very small needle once a day. If labs show that one of the lab tests (parathyroid hormone) is above a certain level an additional medication cinacalcet will be added to the treatment regimen. Cinacalcet is a pill taken by mouth once a day and the dose will be adjusted as needed.

Normal or High Bone Turnover Arm:

Patients in the normal or high bone turnover arm who are receiving the study medication will be taking alendronate. This medication is a pill taken by mouth once a week on an empty stomach with 6-8 ounces of water. After swallowing the medication you should not lie down for 30 minutes. Study visits are listed below:

Visit 1 – Baseline: You will have a Quantitative Computed Tomography (QCT) and a mammogram of your wrist, and blood drawn. QCT is an X-ray test that measures bone mineral density, a Multi-Detector Computerized Tomography (MDCT) which is a computerized X- ray test that measures calcium deposits on the lining of your heart's arteries. The mammogram of the wrist measures calcium deposits with in the media of the peripheral arteries. Blood drawn for bone markers to determine turnover and for biochemical tests for monitoring. Serum pregnancy tests will be performed prior to QCT for females of childbearing potential.After the baseline visit once the results of markers for turnover assessment are received we will visit with you in your dialysis unit to discuss which treatment group you will be in and if you will be receiving active treatment or standard of care.

Visit 2 – One Week +/- 3 days after starting treatment: You will have safety and monitoring blood draw.

Visit 3 – Two weeks +/- 3 days after starting treatment: You will have safety and monitoring blood draw and bone markers for turnover.

Visit 4 – One Month +/- 3 days after starting treatment: You will have safety and monitoring blood draw and bone markers.

Visit – 5 Three Months +/- 3 days after starting treatment: You will have safety and monitoring blood draw and bone markers for turnover.

Visit 6 – Six Months +/- 3 days after starting treatment: You will have DXA, QCT/MDCT, wrist mammogram safety and monitoring blood draw and bone markers for turnover.

Visit 7 – Nine Months +/- 3 days after starting treatment: You will have safety and monitoring blood draw and bone markers for turnover.

Visit 8 – 12 Months +/- 3 days after starting treatment: You will have DXA, QCT/MDCT, wrist mammogram, safety and

monitoring blood draw and bone markers for turnover.

Visit 9 – 15 Months+/- 3 days after starting treatment: You will have safety and monitoring blood draw and bone markers.

Visit 10 – 18 Months +/- 3 days after starting treatment: You will have DXA, QCT/MDCT, wrist mammogram safety and monitoring blood draw and bone markers for turnover.

Visit 11 – 21 Months+/- 3 days after starting treatment: You will have safety and monitoring blood draw and bone markers.

Visit 12 – 24 Months +/- 3 days after starting treatment: You will have DXA, QCT/MDCT, wrist mammogram, safety and monitoring blood draw and bone markers for turnover.

At every study visit: A member of the study team will ask you questions about your medical history, medications, any ongoing or new illnesses, and doctor visits or hospitalizations. You will also receive phone calls at least monthly to record any issues that you are having.

Additional Safety Visits: Additional visits for safety and monitoring blood draw may be needed based on lab results and could be added in addition to the above visits.

Additional Visits: Additional DXA, QCT/MDCT, wrist mammogram, safety and monitoring blood draw and bone markers may be collected at end of enrollment in the case of anticipated early withdraw.

If you are randomly assigned to the standard of care group and are not receiving treatment you will only need to complete the baseline and 12 month visits, but will still receive monthly phone calls to record any issues that you are having.

Visit Type	DX A	QCT/MDCT/ mammogram	Safety and Monitoring Blood Draw	Bone Markers for Turnover Assessment Blood Draw
Screening	X			
Visit 1 - baseline		X	X	X
Visit 2 – 1 week +/- 3 days after starting treatment			X	
Visit 3 – 2 weeks +/- 3 days after starting treatment			X	X
Visit 4 – 1 Month +/- 3 days after starting treatment			X	X
Visit 5 – 3 Months +/- 3 days after starting treatment			X	X
Visit 6 – 6 Months +/- 3 days__after starting treatment	X	X	X	X

Visit 7 – 9 Months +/- 3 days after starting treatment			X	X
Visit 8 – 12 Months+/- 3 days after starting treatment	X	X	X	X
Visit 9 – 15 Months+/- 3 days after starting treatment			X	X

Visit 10 – 18 Months +/- 3 days after starting treatment	X	X	X	X
Visit 11 – 21 Months+/- 3 days after starting treatment			X	X
Visit 12 – 24 Months +/- 3 days after starting treatment	X	X	X	X

WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS?

Risks of Procedures

Blood Draw: Whenever blood is drawn, there is a small risk of soreness, bruising, pain, infection, fainting, and bleeding.

MDCT, QCT, mammogram and DXA: Like all radiographic techniques the measurement of bone mass exposes you to some radiation. The radiation doses for DXA, mammogram and MDCT are small and similar to what you are exposed to everyday in the environment. The radiation dose from a typical DEXA bone scan produces approximately 1/300th of the natural background radiation dose we receive each year. This radiation dose would not be considered to be a significant risk of any harmful effects. Each CT scan will give a radiation dose greater than that from a typical natural background exposure, but less than the limit for radiation workers and well below the levels that are considered to be a significant risk of any harmful effects. In addition, you may feel claustrophobic during the QCT or MDCT test.

While participating in the study, you are expected to follow all study procedures and take all medication as prescribed. In addition, you should not take part in any other research project without approval from Dr. Malluche or a member of the study team. This is to protect you from possible injury arising from such things as extra blood drawing, interaction of research drugs, or similar hazards.

Risks of Medications:

Both teriparatide and alendronate have been used in osteoporotic patients for more than 11 and 15 years, respectively. In the experience of the PI they are generally well-tolerated. The PI has used these medications in his osteoporosis practice in patients with and without chronic kidney disease (CKD) for over 10 years and has experience in long-term monitoring of these treatments. Cinacalcet is approved for dialysis patients. In a double blind placebo controlled trial of cinacalcet in 3,861 patients, there were no differences in serious or non-serious adverse events among the over 1,000 events tracked for those receiving the drug versus those receiving placebo (non-active drug). There is limited experience regarding the administration of teriparatide and cinacalcet together to dialysis patients and the toxicities of the combination are unknown.

Alendronate:

Possible Risk/Side Effect	How often has it occurred?	How serious is it?	Can it be corrected?
GI complaints (abdominal pain, nausea, dyspepsia(heartburn), constipation, diarrhea, and flatulence)	Occasionally	Minimal	Yes, by stopping the medication
More Severe GI Complaints; (Regurgitation, esophageal ulcer, vomiting, dysphagia (difficulty swallowing), abdominal distention, and gastritis)	Less Often	Can be serious	Yes, by stopping the medication but in some instances may require treatment.
Taste Perversion	Rarely	Minimal	Yes by stopping the medication
Low blood levels of calcium and phosphorus	Occasionally, usually transient	Mild, asymptomatic	Yes, by stopping the medication
Bone, muscle, or joint pain	4% of patients	Minimal	Yes, by stopping the medicaiton
Osteonecrosis of the Jaw	Rarely	Serious	May require treatment
Femur and subtrochanteric insufficiency (spontaneous thigh bone) fractures	Rarely and is associated with long term use of more than 5 years	Serious	May require treatment

Teriparatide:

Possible Risk/Side Effect	How often has it occurred?	How serious is it?	Can it be corrected?
Arthralgia/pain	Occasionally	Minimal	Yes, by stopping the medication
Nausea	Occasionally	Minimal	Yes, by stopping the medication
Dizziness	Occasionally	Minimal	Yes by stopping the medication
Leg cramps	Occasionally	Minimal	Yes, by stopping the medication
Injection site reaction	Occasionally	Minimal	Yes, by stopping the medicaiton

High blood calcium	Rarely	Can be serious	Yes, by stopping the medication
Osteoscarcoma (Cancer of the bone)	Rare – Incidence in the normal population is 1 out of 400,000 and only 3 cases have been reported in the 1.2 million patients taking the medication.	Very Serious	Will need treatment

Cinacalcet:

Possible Risk/Side Effect	How often has it occurred?	How serious is it?	Can it be corrected?
Hypocalcemia (low blood calcium)	Occasionally	Can be serious	Yes, by stopping the medication
Nausea	Occasionally	Minimal	Yes, by stopping the medication
Vomiting	Occasionally	Minimal	Yes by stopping the medication
Diarrhea	Occasionally	Minimal	Yes, by stopping the medication
Myalgia (muscle pain)	Occasionally	Minimal	Yes, by stopping the medicaiton
Dizziness	Rarely	Minimal	Yes, by stopping the medication
Hypertension	Less often	Can be serious	Yes, by stopping the medication

There is always a chance that any medical treatment can harm you, and the investigational treatment in this study is no different. In addition to the risks listed above, you may experience a previously unknown risk or side effect.

WILL YOU BENEFIT FROM TAKING PART IN THIS STUDY?

There is no guarantee that you will get any benefit from taking part in this study. If you are assigned to a treatment group there is the possibility that you may have improvement in your bone density as well as less progression of calcium deposits in your heart. Moreover your willingness to take part may, in the future, help doctors know what method is best to treat bone loss in patients on dialysis.

DO YOU HAVE TO TAKE PART IN THE STUDY?

If you decide to take part in the study, it should be because you really want to volunteer. You will not lose any benefits or rights you would normally have if you choose not to volunteer. You can stop at any time during the study and still keep the benefits and rights you had before volunteering. If you decide not to take part in this study, your decision will have no effect on the quality of medical care you receive.

IF YOU DON'T WANT TO TAKE PART IN THE STUDY, ARE THERE OTHER CHOICES?

If you do not want to take part in the study, you can discuss bone loss with your primary physician or nephrologist and continue with standard of care treatment. Standard of care treatment for patients with your condition includes yearly bone density monitoring and maintaining normal levels of Vitamin D, phosphorus, and parathyroid hormone.

WHAT WILL IT COST YOU TO PARTICIPATE?

You and/or your insurance company, Medicare or Medicaid will be responsible for the costs of all care and treatment you receive during this study that you would normally receive for your condition. These are costs that are considered medically reasonable and necessary and will be part of the care you receive if you do not take part in this study.

The University of Kentucky is not allowed to bill your insurance company, Medicare or Medicaid for the medical procedures done strictly for research. . Therefore, the nephrology department has agreed to pay all research-related costs including paying for the study medications alendronate, cinacalcet, and teriparatide as well as the DXA, QCT, and MDCT radiographic studies and all blood tests related to the study during the time of enrollment in the research study.

WHO WILL SEE THE INFORMATION THAT YOU GIVE?

We will keep private all research records that identify you to the extent allowed by law. Your information will be combined with information from other people taking part in the study. When we write about the study to share it with other researchers, we will write about the combined information we have gathered. You will not be personally identified in these written materials. We may publish the results of this study; however, we will keep your name and other identifying information private. We will collect your social security number for reimbursement purposes only.

We will make every effort to prevent anyone who is not on the research team from knowing that you gave us information, or what that information is. Your information on paper records will be kept under lock and key in the office of the study coordinators. Computer records will be kept on a password protected computer in the study coordinator's office.

You should know, however, that there are some circumstances in which we may have to show your information to other people. For example, the law may require us to show your information to a court or to tell authorities if you report information about a child being abused or if you pose a danger to yourself or someone else. If you earn $600 or more by participating in any research, it is potentially reportable for tax purposes. Officials of the Food and Drug Administration, the National Institutes of Health, and the University of Kentucky may look at or copy pertinent portions of records that identify you.

CAN YOUR TAKING PART IN THE STUDY END EARLY?

If you decide to take part in the study you still have the right to decide at any time that you no longer want to continue. You will not be treated differently if you decide to stop taking part in the study.

The individuals conducting the study may need to withdraw you from the study. This may occur if you are not able to follow the directions they give you, if they find that your being in the study is more risk than benefit to you, or if the agency funding the study decides to stop the study early for a variety of scientific reasons. If you withdraw or are withdrawn, the study drug will no longer be provided to you free of charge and may not be available commercially.

ARE YOU PARTICIPATING OR CAN YOU PARTICIPATE IN ANOTHER RESEARCH STUDY AT THE SAME TIME AS PARTICIPATING IN THIS ONE?

You may not take part in this study if you are currently involved in another research study. It is important to let the investigator/your doctor know if you are in another research study. You should also discuss with the investigator before you agree to participate in another research study while you are enrolled in this study.

WHAT HAPPENS IF YOU GET HURT OR SICK DURING THE STUDY?

If you believe you are hurt or if you get sick because of something that is due to the study, you should call Dr. Malluche at 859-323-2637 immediately. Dr. Malluche will determine what type of treatment, if any, that is best for you at that time. You may also call the study coordinator who is a certified physician assistant at the cell phone 859-619-5304.

It is important for you to understand that the University of Kentucky does not have funds set aside to pay for the cost of any care or treatment that might be necessary because you get hurt or sick while taking part in this study. Also, the University of Kentucky will not pay for any wages you may lose if you are harmed by this study.

The medical costs related to your care and treatment because of research related harm may be paid by your insurer if you are insured by a health insurance company (you should ask your insurer if you have any questions regarding your insurer's willingness to pay under these circumstances); or may be paid by Medicare or Medicaid if you are covered by Medicare, or Medicaid (if you have any questions regarding Medicare/Medicaid coverage you should contact Medicare by calling 1-800-Medicare (1-800-633-4227) or Medicaid 1-800-635-2570.

A co-payment/deductible from you may be required by your insurer or Medicare/Medicaid even if your insurer or Medicare/Medicaid has agreed to pay the costs). The amount of this co-payment/deductible may be substantial. You do not give up your legal rights by signing this form.

WILL YOU RECEIVE ANY REWARDS FOR TAKING PART IN THIS STUDY?

You will receive $150.00 for each scan visit to UK and $20 for any visits during your dialysis session. Payment will be made by mailing a check after each visit. Travel pay will be reimbursed at the currently approved Mileage Reimbursement Rate.

WHAT IF YOU HAVE QUESTIONS, SUGGESTIONS, CONCERNS, OR COMPLAINTS?

Before you decide whether to accept this invitation to take part in the study, please ask any questions that might come to mind now. Later, if you have questions, suggestions, concerns, or complaints about the study, you can contact the investigator, Hartmut Malluche, MD at 859-323-2637. If you have any questions about your rights as a volunteer in this research, contact the staff in the Office of Research Integrity at the University of Kentucky between the business hours of 8am and 5pm EST, Mon-Fri at 859-257-9428 or toll free at 1-866-400-9428. We will give you a signed copy of this consent form to take with you.

WHAT IF NEW INFORMATION IS LEARNED DURING THE STUDY THAT MIGHT AFFECT YOUR DECISION TO PARTICIPATE?

If the researcher learns of new information in regards to this study, and it might change your willingness to stay in this study, the information will be provided to you. You may be asked to sign a new informed consent form if the information is provided to you after you have joined the study.

WHAT ELSE DO YOU NEED TO KNOW?

There is a possibility that the data collected from you may be shared with other investigators in the future. If that is the case the data will not contain information that can identify you unless you give your consent/authorization or the UK Institutional Review Board (IRB) approves the research. The IRB is a committee that reviews ethical issues, according to federal, state and local regulations on research with human subjects, to make sure the study complies with these before approval of a research study is issued. The Department of Nephrology is providing financial support and/or material for this study.

AUTHORIZATION TO USE OR DISCLOSE YOUR IDENTIFIABLE HEALTH INFORMATION

The privacy law, HIPAA (Health Insurance Portability and Accountability Act), requires researchers to protect your health information. The following sections of the form describe how researchers may use your health information.

Your health information that may be accessed, used and/or released includes:

- Name
- Demographics
- Date of birth
- Social Security Number
- Dates of visit at the UK hospital
- Medical history
- Medications
- Results of laboratory tests
- Results of bone X-rays
- Death Certificates
- Hospital and Clinic Notes pertaining to the study

The Researchers may use and share your health information with:

- The University of Kentucky's Institutional Review Board/Office of Research Integrity.
- Law enforcement agencies when required by law.
- UK Hospital or University of Kentucky representatives if applicable.
- National Institutes of Health
- Center for Clinical and Translational Science (CCTS)
- Department of Radiology
- Food and Drug Administration
- Gill Heart Institute
- Your primary physician will be contacted if researcher in the course of the project learns ofa medical condition that needs immediate attention.
- Investigational Drug Service (IDS)

The researchers agree to only share your health information with the people listed in this document.

Should your health information be released to anyone that is not regulated by the privacy law, your health information may be shared with others without your permission; however, the use of your health information would still be regulated by applicable federal and state laws.

You will not be allowed to participate in the research study if you do not sign this form. If you decide not to sign the form, it will not affect your:

- Current or future healthcare at the University of Kentucky
- Current or future payments to the University of Kentucky
- Ability to enroll in any health plans (if applicable)

- Eligibility for benefits (if applicable)

After signing the form, you can change your mind and NOT let the researcher(s) collect or release your health information (revoke the Authorization). If you revoke the authorization:

- You will send a written letter to: Dr. Malluche, Division of Nephrology, UK Medical Center, 800 Rose St, Room MN 564, Lexington, KY, 40536-0298 to inform him of your decision.
- Researchers may use and release your health information **already** collected for this research study.
- Your protected health information may still be used and released should you have a bad reaction (adverse event).
- You may not be allowed to participate in the study.

The use and sharing of your information has no time limit.

If you have not already received a copy of the Privacy Notice, you may request one. If you have any questions about your privacy rights, you should contact the University of Kentucky's Privacy Officer between the business hours of 8am and 5pm EST, Mon-Fri at: (859) 323-1184.

_____ _____

Signature of research subject Date

_____

Printed name of research subject

_____ _____

Name of person obtaining informed consent/HIPAA authorization Date

_____

Signature of Principal Investigator or Sub/Co-Investigator

Statistical Analysis

Sample Size Analysis: We used pilot data from 105 patients (30 Non-High and 75 High bone turnover) which demonstrated a decline of 10-12 units total hip BMD by QCT (TH-QCT) during follow-up (specifically: 11.9 ±14.4 Non-High and 10.1 ± 20.4 High turnover). A sample of 15 patients per treatment arm (drug and placebo arms) in the Non-High turnover trial and 21 patients per treatment arm in the High bone turnover trial have at least 88% power in each trial to detect a 10-point improvement with treatment (two tailed T-test at the 0.05 level).

Binary and categorical variables are reported as counts and proportions. Continuous variables are reported as means and standard deviations. The primary outcome was change in QCT total hip BMD (g/cm^3) over 1 year. Secondary outcomes were change in the square root of vascular calcifications of the aorta and coronary arteries, as well as survival. Outcomes were compared between treatment groups within turnover arms, and between turnover arms using t-tests. Multivariable regression was used to assess group differences with adjustment for imbalanced covariates, primarily race. Survival differences were assessed via log-rank tests using the Kaplan-Meier method. Significance was set at $p < 0.05$. All statistics were calculated using SPSS® version 28 (IBM® Corp., Armonk, NY).