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IRB_00073750 **Created:** 5/7/2014 3:28 PM

PI: IRB Administrator **Submitted:** 6/3/2014

Title: Exemption Umbrella: Assessment of Nutrition, Cardiovascular Disease, and Metabolism in CKD

1. Contacts and Title

1. Principal Investigator:

IRB Administrator

Email	Training	CoI Date
irb@hsc.utah.edu		

a. Position of Principal Investigator:

- (•) **Faculty**
- ( ) Student
- ( ) Staff
- ( ) Resident/Fellow
- ( ) Other

If Other, describe:

b. Will the Principal Investigator consent participants? ( ) Yes (•) **No**

2. Contact Person(s) (if different from the PI):

Name	Email	Training

There are no items to display

3. Internal Staff and Sub-Investigator(s) (Within the University of Utah):

Name	Email	Training	Obtaining Consent	CoI Date

There are no items to display

4. External Sub-Investigator(s) (Investigators outside the University of Utah):

Last Name	First Name	Affiliation

There are no items to display

5. Faculty Sponsor (if needed):

6. Guests:

Last Name	First Name	E-Mail

There are no items to display

7. What type of application is being submitted?

New Study Application (or Amendment/Continuing Review)

8. Title Of Study:
Exemption Umbrella: Assessment of Nutrition, Cardiovascular Disease, and Metabolism in CKD

9. Study Purposes and Objectives:

This is a submission for an umbrella protocol that will cover all data querying and secondary data and tissue analyses procedures by the investigators on this application. The aim of each secondary data and tissue analyses performed under this application is to examine nutrition, cardiovascular disease, and metabolism in chronic kidney disease.

This umbrella protocol meets the criteria for University of Utah **IRB Exemption Category 4:**

Research involving the collection or study of existing data, documents, records, pathological specimens or diagnostic specimens, if these sources are publicly available or the information is recorded by the investigator in such a manner that the subjects cannot be identified

directly or through identifiers linked to the subjects. AND

1. *The research is not subject to FDA regulations.*
2. *The research does not involve prisoners as participants.*
3. *The research meets the University's ethical standards governing the conduct of the research.*

A database and biorepository exist to house the data and samples from the following protocols, and this database will be used for future secondary data and tissue analyses under this umbrella:

1. Adipokines in Hemodialysis Patients (IRB_00028427)
2. Effects of Febuxostat on Adipokines and Kidney Disease in Diabetic CKD (IRB_00044016)
3. Effects of oral calcium carbonate therapy on serum fibroblast growth factor 23, markers of inflammation and oxidative stress in CKD patients with high phosphaturia: a cross-over open label study. (IRB_00044173)
4. Ergocalciferol therapy in calcidiol deficient, hemodialysis patients on therapeutic doses of paricalcitol (IRB_00064582)
5. Protein intake, nutrition and cardiovascular disease in stage V CKD (IRB_00024816)
6. Protein Supplementation in Dialysis Patients (IRB_00064579)
7. Lipolysis in hemodialysis (IRB_00042953)

None of these protocols are currently funded by federal or non-federal agencies; however, some received federal funding at specific periods during the conduct of the study.

10. Background and Introduction:

The studies included in this umbrella protocol explore the relationship between chronic kidney disease and nutrition, cardiovascular disease, and metabolism. These issues are closely intertwined and provide a logical basis for the consolidation of these studies into this umbrella protocol.

The relevant background information for these studies are organized into the three key elements of this umbrella protocol: 1. Nutrition 2. Cardiovascular Disease and 3. Metabolism

I. NUTRITION

Poor nutritional status as evidenced by low body mass index, low muscle mass or low serum albumin is a strong predictor of morbidity and mortality in dialysis patients. This umbrella protocol reviews three key factors that can impact nutrition to better understand the impact of nutrition on morbidity and mortality in dialysis patients.

1. Inflammation

Hypercatabolism induced by inflammation is widely considered the cause of uremic malnutrition even though there is no clear evidence that hemodialysis patients with elevated C-reactive protein (CRP) levels are at greater risk of losing weight or muscle mass.

Adipokines are protein hormones produced by the adipocytes. These include tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), plasminogen activator inhibitor (PAI-1), leptin, angiotensinogen and adiponectin and serve as the signals for the effects of adipocytes on insulin resistance, dyslipidemia, hypertension, inflammation and atherosclerosis.

In obesity, the production of TNF-α, IL-6, PAI-1, leptin and angiotensinogen increases whereas the production of adiponectin decreases. Increased expression of pro-inflammatory TNF-α and IL-6 and decreased expression of anti-inflammatory adiponectin by adipocytes might be associated with insulin resistance, inflammation and oxidative stress. In addition, as insulin resistance, inflammation and oxidative stress are considered major contributors of hypercatabolism in uremia , interventions to modulate adipose tissue adipokine expression might reduce insulin resistance, inflammation and oxidative stress and improve nutritional status.

2. Vitamin D

Vitamin D has long been known to possess immuno-regulatory activities. Studies using cells derived from PBMC showed that 'inactive', precursor 25 $(OH)D_3$ can readily act as an immunosuppressive agent after local activation to 1,25 $(OH)_2$ D_3. Vitamin D down-regulates nuclear factor-kB activity, increases IL-10 production and decreases IL-6, IL-12, IFN-γ, and TNF-α production, leading to a cytokine profile which favors less inflammation .

In the general population, calcidiol deficiency has been shown to be associated with inflammation, insulin resistance, proteinuria and mortality . However, in the CKD and dialysis populations, most of the studies have examined the role of active vitamin D_3 (calcitriol) or its analogue (paricalcitol) or vitamin D_2 analogue (doxercalciferol). In a landmark study of the Fresenius database, it was shown that therapy with paricalcitol (brand name "Zemplar"), an analogue of calcitriol, was associated with better survival compared to calcitriol treated hemodialysis (HD) patients]. More recent studies have suggested that therapy with any active vitamin D in CKD and HD patients was associated with a survival benefit compared to no vitamin D treatment . Nonetheless, it remains unclear whether calcidiol deficiency in active Vitamin D treated HD patients is associated with inflammation and insulin resistance and whether treatment of calcidiol deficiency will improve these conditions in HD patients.

3. Body Composition

There is little data on whether dialysis patients with malnutrition and elevated C-reactive protein levels would gain muscle mass with protein supplementation.

Even though the National Kidney Foundation guidelines recommend a dietary protein intake of 1.2 g/kg/d in hemodialysis patients, it remains unclear whether high protein intake has beneficial or harmful nutritional and cardiovascular effects in this population. Our earlier data suggest that high protein intake might improve nutritional status but it has been argued that the state of low muscle mass, small body size and low serum protein levels is not the result of decreased dietary intake, rather hypercatabolism induced by metabolic acidosis, inflammation and oxidative stress . Therefore, a high protein intake in these patients might be harmful by worsening metabolic acidosis without improving nutritional status. The effects of protein intake on cardiovascular disease are also controversial.

Malnutrition has been considered to be a cardiovascular risk factor primarily because malnutrition is strongly associated with cardiovascular death in dialysis patients . On the other hand, it has also been suggested that high protein intake might result in hyperphosphatemia, hence increased serum calcium x phosphorus product and arterial calcification with the attendant consequences of arterial stiffness, myocardial stress and decreased diastolic filling of coronary arteries, myocardial ischemia and cardiovascular events. The relative risks and benefits of high dietary protein intake in hemodialysis patients are therefore unresolved.

II. CARDIOVASCULAR DISEASE

In seeking to better understand the association of chronic kidney disease and cardiovascular disease,

this umbrella protocol looks at three factors proposed to be linked to cardiovascular disease.

Fibroblastic Growth Factor – 23 (FGF)-23:

Disorders of mineral and bone metabolism are common complications of chronic kidney disease (CKD). The damaged kidneys are unable to completely excrete dietary phosphorus load, leading to compensatory secondary hyperparathyroidism with elevated intact-PTH (iPTH), decreased levels of 1,25-dihydroxyvitamin D and elevated levels of recently discovered phosphaturic molecule fibroblastic

growth factor (FGF)-23 in order to promote phosphaturia and maintain normal serum phosphorus level.

Serum FGF-23 levels were found to be elevated in early stages of CKD, even before phosphorus levels were elevated, and the serum levels of FGF-23 increase as the GFR declines. There is some evidence to suggest that elevated serum levels of FGF-23 are not only the results of worsening kidney function but also most likely contributes to accelerated atherosclerosis and mortality in CKD It has been proposed that targeting levels of elevated serum FGF23 in normophosphatemic CKD patients may improve outcomes in CKD.

However, elevated serum FGF23 levels in non-CKD population also predict poor cardiovascular outcomes[8]. Therefore, it is unclear whether elevated FGF23 levels are unique to the phosphorus homeostasis in CKD. We propose that elevated FGF23 levels correlate with urine phosphate excretion, and also with markers of oxidative stress and inflammation. Better understanding of these processes may allow interventional studies with phosphate binders.

Hyeruricemia

In contrast to the associations of high body mass index (BMI) with increased mortality in the general population, high BMI is associated with better survival in dialysis patients . Hence, obesity is considered protective in dialysis patients. This raises the question whether uremia impairs the molecular signaling pathways that mediate the effects of adipocytes on insulin resistance, dyslipidemia, hypertension, inflammation and atherosclerosis in the general population.

Hyperuricemia is highly prevalent in the US population and commonly clusters with obesity and metabolic syndrome. It remains controversial whether this reflects an epiphenomenon or connotes a causal role of hyperuricemia in metabolic syndrome. If indeed hyperuricemia plays a causal role in metabolic syndrome, it would be expected that hyperuricemia will impact the molecular signals that mediate the effects of adiposity on inflammation and insulin resistance.

Adipokines, the protein hormones produced by the adipocytes, serve as the signals for the effects of adipocytes on insulin resistance, dyslipidemia, hypertension, inflammation and atherosclerosis . Adipokines include tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), plasminogen activator inhibitor (PAI-1), leptin, angiotensinogen and adiponectin. In obesity, the production of TNF-α, IL-6, PAI-1, leptin and angiotensinogen increases whereas the production of adiponectin decreases. Increased expression of pro-inflammatory TNF-α and IL-6 and decreased expression of anti-inflammatory adiponectin by adipocytes results in insulin resistance and inflammation.

As oxidative stress in adipose tissue is considered to play a critical role in dysregulation of adipokines production in obesity and that hyperuricemia induces oxidative stress in adipocytes , we hypothesize that hyperuricemia alters adipose tissue production of adipokines ; therefore, febuxostat therapy will decrease hyperuricemia and thereby, have beneficial effects on adipokine production by adipose tissue; the favorable effects on adipokine production by febuxostat therapy will result in decrease in plasma levels of markers of inflammation; and as a result of the above, urinary markers of kidney disease will improve.

METABOLISM

Overview of lipolysis:

Adipose tissue stores fatty acids in the form of triglycerides (TGs) as a source of energy. Adipose tissue lipolysis is the process by which the stored fatty acids are released leading to decrease in fat mass . Hydrolysis of TGs in adipose tissue is catalyzed by hormone-sensitive lipase (HSL) and monoglyceride lipase (MGL).HSL alone catalyzes the hydrolysis of TGs and diglycerides (DGs), whereas the participation of MGL is required to obtain complete hydrolysis of monoglycerides (MGs). HSL is the rate-limiting step in lipolysis.

The adipose tissue lipolytic effects of HSL are countered by lipoprotein lipase (LPL) that promotes fatty acid storage. LPL anchored on endothelial cell surface in fat (and other) tissues catalyzes the cleavage of fatty acids from triglyceride-rich lipoproteins in the plasma, making the released fatty acids available for uptake by adipocytes for energy storage. The end effect of LPL in fat tissues is the enhancement of fat and energy stores. In several physiological situations, such as pregnancy, lactation, hibernation, and fasting, a reciprocal regulation between HSL and LPL in adipose tissue has been demonstrated . Studies performed in pregnant rats have shown that during the anabolic phase, HSL-to-LPL mRNA and activity ratios are low, whereas this ratio increases during the catabolic phase . Thus, HSL-to-LPL ratios provide an accurate indication of catabolism or anabolism of fat at the tissue level and should be useful in the understanding of fat tissue metabolism and weight gain/loss in dialysis patients. This apparently important area of metabolism and nutrition has not been explored in this unique population.

Factors affecting lipolysis:

1. Catecholamines: Lipolysis is controlled mainly by the activity of the sympathetic nervous system and by plasma insulin levels . Activation of lipolysis is mediated by an increment of intracellular cAMP concentrations and activation of PKA.

2. Insulin: Insulin is the most important physiological inhibitor of catecholamine-induced lipolysis, induces phosphorylation and activation of the phosphodiesterase type 3B, leading to a decrease in cAMP levels and concomitant decrease of PKA activity .

3. TNF*a*: The lipolytic effect of TNF*a* could be explained by the decrease in LPL activity and intracellular reesterification rates and/or down-regulation of perilipin expression .

4. Zinc-alpha(2)-glycoprotein (ZAG) and lipid-mobilizing factor (LMF): Loss of adipose tissue in cancer cachexia has been associated with tumour production of a lipid-mobilizing factor (LMF) which has been shown to be homologous with the plasma protein zinc-alpha(2)-glycoprotein (ZAG) . Bing et al showed that ZAG is produced by adipose tissue, and the mRNA and protein levels of ZAG are markedly increased in adipose tissue of mice with cancer cachexia . ZAG may play an important role in the local modulation of lipid metabolism and contribute particularly to the substantial reduction of adipose in cancer cachexia by inducing uncoupling proteins Both LMF and ZAG molecules induce lipolysis *in vitro* by a cAMP-mediated system through interaction with a β_3-adrenoreceptor. ZAG purified from human plasma was shown to stimulate glycerol release from isolated murine epididymal adipocytes in a dose-dependent manner . Body composition analysis showed that loss of body weight in ZAG administered mice could be attributed entirely to the loss of body fat . ZAG knockout mice were overweight with respect to wild-type littermates

Adipose tissue lipolysis in uremia:

Low body weight is a well known risk factor for increased mortality in dialysis patients ~~(12)~~. Further, loss of weight has been associated with increased mortality in dialysis patients ~~(2)~~. However, there is a paucity of data on whether uremia by itself promotes adipose tissue lipolysis and the mechanisms of adipose tissue lipolysis in dialysis patients. It is conceivable that uremia results in increased plasma catecholamines, insulin resistance and inflammation which could all stimulate adipose tissue lipolysis.

Even though, as discussed above, data from cancer literature suggest an important role for ZAG in cancer cachexia, it is virtually unknown whether ZAG levels are elevated in dialysis patients and whether this contributes to uremic wasting syndrome.

The mechanisms of lipolysis in uremia are virtually unknown. Understanding these mechanisms might have therapeutic implications for treating uremic wasting syndrome. Furthermore, identifying the mechanisms of fat wasting in uremia might have therapeutic implications for combating the substantial morbidity and mortality associated with the obesity epidemic in the US general population.

2. Study Location and Sponsors

2. Study Location and Sponsors

1. **Department:**
   INTERNAL MEDICINE
2. **Location of Study:**

   University of Utah's Covered Entity (Health sciences, hospitals, and clinics)
3. **Is this a Multicenter Study (i.e., the study involves other sites with other PIs):**

   ○ Yes ◉ **No**

   a. **If yes, are you the lead investigator of this study, or is this the central location for the study?**

      ○ Yes ◉ **No**
4. **Indicate other locations that are participating in the study for which you, as the PI, are responsible:**

Site Name	Other Site	Site Investigator	Investigator/Main Contact

There are no items to display

   a. **How will adverse events, unanticipated problems, interim results, and changes to the research be communicated between the participating sites and the Principal Investigator?**
5. **Indicate the source(s) of funding obtained or applied for to support this study.**

Sponsor	Sponsor Type	Sponsor Contact Information

There are no items to display
6. **Does this study have functions assigned to a Contract Research Organization (CRO)?**
   ○ Yes ◉ **No**

   If yes, CRO Contact Information:
7. **Does this study involve use of the Utah Population Database (UPDB)?**
   ○ Yes ◉ **No**

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3. Participants

1. **Ages of Participants:**
   18 and older (Consent form needed)
2. **Specific age range of participants (e.g., 7-12 years old, 60+, etc.):**
   18+
3. **Indicate any vulnerable participant groups (other than children) included:**

   None

   If "Other", please specify:

   If "None" and no children are involved, answer the following question.
   Has the participant selection process overprotected potential subjects who are considered vulnerable so that they are denied opportunities to participate in research?
   ○ Yes ◉ **No**
4. **Number of participants to be enrolled during the entire study:**

   At Utah: 2000

   All Centers: 2000
5. **Characteristics of Participants/Inclusion Criteria:**

   Participants will have met the following inclusion criteria for the study in which they were enrolled. Data and tissue for eligible, enrolled individuals are included in the database and biorepository and will be available for queries for future secondary analyses.

   1. Adipokines in Hemodialysis Patients (IRB_00028427): This study has an interventional and observational component.

   For the RCT: 100 overweight (BMI 25.0 - 29.9 kg/m^2) or obese (BMI ≥ 30kg/m^2) adult prevalent chronic hemodyalsis patients with diabetes or insulin resistance will be randomized. Homeostatic Model of Assessment of Insulin Resistance (HOMA-IR) will be used and those with HOMA

> 2.1 will be considered to have insulin resistance.

In addition, to serve as health controls for the Western blot and PCR analyses of the subcutaneous adipose tissue 10 kidney transplant donors will be recruited.

For the observational component:

20 normal BMI hemodialysis patients and 25 overweight/obese hemodialysis patients without insulin resistance.

20 normal BMI and 20 overweight/obese patients undergoing surgical procedures.

2. Effects of Febuxostat on Adipokines and Kidney Disease in Diabetic CKD (IRB_00044016): Age > 18 years, diagnosis of type 2 diabetes, serum uric acid ≥ 5.5 mg/dl in men and ≥ 4.6 mg/dl in women, and kidney disease defined as eGFR 30-60mL/min/1.73m^2 by 4-variable MDRD or eGFR > 60mL/min/1.73m^{2}with urine dipstick ≥ 1+ proteinuria or urine albumin/creatinine ≥ 30mg/g

3. Effects of oral calcium carbonate therapy on serum fibroblast growth factor 23, markers of inflammation and oxidative stress in CKD patients with high phosphaturia: a cross-over open label study. (IRB_00044173): Age > 18, CKD stages III and IV patients (defined as estimated MDRD GFR 15 to 60 ml/min/1.73m^2) with elevated urinary phosphate excretion (defined as urine phosphorus/creatinine ratio > 800mg of phosphorus/g of creatinine) and high normal serum phosphor0us levels (defined as serum phosphorus concentration 3.8-5.5 mg/dl).

4. Ergocalciferol therapy in calcidiol deficient, hemodialysis patients on therapeutic doses of paricalcitol (IRB_00064582): Chronic kidney disease stage 5 patients on hemodialysis which includes both diabetic as well as non-diabetic patients on hemodialysis, hsCRP > 3 mg/dl, on stable dose of paricalcitol supplements for at least 3 months with iPTH in target range.

5. Protein intake, nutrition and cardiovascular disease in stage V CKD (IRB_00024816): The study will be comprised of adult (18+ years) chronic hemodialysis patients. Appetite often changes with the initiation of dialysis and kidney function recovers sometimes from acute renal failure; hence only patients on dialysis at least for three months will be included.

6. Protein Supplementation in Dialysis Patients (IRB_00064579): This study consists of men and women (age ≥ 18 years) on hemodialysis for at least 3 months with inflammation (hsCRP > 3mg%) and either BMI < 23kg/m^{2}or low muscle mass as evident by serum creatinine < 8mg% in the presence of anuria (urine output < 200 ml/d) and adequate dialysis (URR > 65%).

7. Lipolysis in hemodialysis (IRB_00042953):

Group 1 (n=10):

-Participant in Protein intake, nutrition, and cardiovascular disease in stage V CKD study.

- unintentional weight loss of at least 2% of body weight for over 6 months.

Group 2 (n=10):

-Participant in Protein intake, nutrition and cardiovascular disease in stage V CKD study

- weight gain of at least 2% of body weight over 6 months

Group 3 (n=10):

-Participant in Protein intake, nutrition and cardiovascular disease in stage V CKD study

- Stable weight over 6 months

Group 4 (n=10):

-Healthy Kidney Transplant Donors

-18 years or older

6. Participant Exclusion Criteria:

Patients were excluded from the following studies based on the exclusion criteria below.

1. Adipokines in Hemodialysis Patients (IRB_00028427):

i. Absolute Exclusion Criteria:

age < 18 years, HOMA ≤ 2.1 in non-diabetics, active liver disease (transaminases >2.5 times the upper limit of normal at baseline), mechanical heart valves because of MRI scans, patients who are unlikely or unable in the opinion of the primary nephrologist to comply with research protocol, patients with Class III or IV New York Heart Association heart failure, macular edema or hard exudates near macula on fundoscopy, current active malignancy (excluding squamous and basal cell skin cancers), active AIDS, chronic lung disease requiring supplemental oxygen therapy, patients enrolled in interventional trials using drugs or devices and anticoagulation therapy (for those undergoing fat biopsy).

Persons with pacemakers and cochlear implants are excluded because of the magnetic field of MRI. Certain types of materials used in breast augmentation could be affected by the strong magnetic field and hence breast augmentation is an exclusion criteria. Artificial hips could interfere with mid-thigh muscle mass measurements whereas lumbar spine hardware could interfere with visceral fat measurements and hence, individuals with these will be excluded. Persons > 300 lbs will be excluded because of the weight limit of the MRI table. Persons who have had a bone break of long bones, vertebrea, or hips in the past three years will be excluded because of the increase risk of fracture seen in patients taking the study medication.

ii. Temporary Exclusion Criteria:

a) TZDs (with the exception of the intervention) will not be allowed during the study period. If the participants are on a TZD at the time of enrollment, another diabetic medication must be substituted and they should be off the TZD for at-least 3 months before they undergo randomization and baseline visit.

b) Patients will be eligible one month after hospitalization

c) Patients will be eligible one month after resolution of clinical signs or symptoms of the infection or completion of antibiotic course (whichever occurs last)

d) Dialysis duration < 3 months. These patients will be eligible after 3 months on dialysis.

e) Inadequate hemodialysis as evidenced by average urea reduction ratio < 65% in preceding three months. These patients will be eligible after their URR improves.

f) Proliferative or pre-proliferative diabetic retinopathy that warrants laser therapy. These patients will be eligible after completion of laser treatments.

2. Effects of Febuxostat on Adipokines and Kidney Disease in Diabetic CKD (IRB_00044016): History of gout, concurrent use of azathioprine, mercaptopurine, theophylline, allopurinol, or warfarin, current antibiotic therapy, pregnant women and prisoners.

3. Effects of oral calcium carbonate therapy on serum fibroblast growth factor 23, markers of inflammation and oxidative stress in CKD patients with high phosphaturia: a cross-over open label study. (IRB_00044173): Known non-compliance with medications and current use of phosphorus binder, patients with identified hypercalcemia Ca level > 10.5.

4. Ergocalciferol therapy in calcidiol deficient, hemodialysis patients on therapeutic doses of paricalcitol (IRB_00064582): Patients not on paricalcitol, enrolled in other interventional studies, hospitalized in the past month or treated for an infection in the past month.

5. Protein intake, nutrition and cardiovascular disease in stage V CKD (IRB_00024816): Patients with persistent volume overload (substantial pedal edema) despite attempts at achieving dry weight will be excluded as hydration status might affect estimation of muscle mass. Further, patients with inability to walk or those who use wheel-chairs might have reduced mid-thigh muscle mass despite good protein intake because of disuse, and hence these patients will be excluded. Patients with significant residual renal function (urine output > 200 ml/day) will be excluded as residual renal function could affect estimation of protein intake from urea kinetic model. Patients who are unlikely or unable (in the opinion of the nephrologists, nurses or dieticians taking care of the patient) to comply with research protocol will be excluded. Patients with symptomatic heart failure, current active malignancy (excluding squamous and basal cell skin cancers) and active AIDS will be excluded. Patients enrolled in intervention trials will be excluded. Patients that have atrial fibrillation implant, pacemaker, cochlear implants, breast augmentation, artificial hip or lumbar spine hardware and any condition that does not allow MRI scanning.

6. Protein Supplementation in Dialysis Patients (IRB_00064579): Unable to give informed consent, prisoner, or pregnant women.

7. Lipolysis in hemodialysis (IRB_00042953): Participant is currently take coumadin.

7. Is a substantial percentage of the participant population anticipated to be non-English speaking?

○ Yes ◉ **No**

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4. Study Information

1. Design of Study (select all that apply):
Secondary/Archival Data Analysis
If Other, describe:

2. Does your study involve the use of any placebo?
○ Yes ◉ **No**

3. Length of entire study, from initiation through closeout: 10 years

4. How will participants be recruited or identified for inclusion in the study?

a. Select all methods that will be used:
Written or electronic record review

b. Describe the recruitment/participant identification process in detail (e.g. who will review charts or records, who can refer participants to the study, where will flyers be posted, how often will recruitment letters be sent, when will follow-up phone calls be made, etc.):

Recruitment for the prospective studies has been completed. This study will use the existing data and tissues from these prospective studies for secondary data and tissue analyses. Queries of this data will be made based on the specific aims of each individual secondary analyses project proposed by the investigator(s).

5. How will consent be obtained?
Waiver or Alteration of Informed Consent

6. Describe all the procedures chronologically, from screening/enrollment through study closeout, which will be completed in the research project.

There are no study procedures to be performed on participants, as this application only proposes to analyze previously-collected data or conduct assays of the already collected samples.

Investigators with a new project that meets the aims of this umbrella will query the database to identify eligible participants and available tissues for the secondary data and tissue analyses. They will use the database and biorepository to record a unique dataset specifically for use in their project. The investigator will be able to see identifiers in the database and biorepository, but will not record identifiers in the unique dataset to be analyzed. This will result in a de-identified dataset for analysis, which will be according to the HIPAA Safe Harbor standards for de-identification. The investigator will not create a code number or other linkage that would allow for re-identification to the identifiers in the database or repository. Tissue samples will be provided to the investigator in a de-identified manner.

7. Are all procedures for research purposes only (non-standard or non-standard of care procedures)?
(•) **Yes** ( ) No

If no, list the procedures that are performed for research purposes only (non-standard or non-standard of care procedures):

8. Is there a safety monitoring plan for this study?
( ) Yes (•) **No**

9. Provide a summary of the statistical methods, data analysis, or data interpretation planned for this study. Factors for determining the proposed sample size (e.g., power) should be stated.

The statistical methods will vary depending upon the type of analyses performed.

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Request for Waiver or Alteration of Consent

Requested Waivers

	Date Created	Type of Request	Purpose of Waiver Request
View	5/28/2014	Waiver of Informed Consent	Secondary data and tissue analyses of existing data and tissues

Request for Waiver or Alteration of Consent

1. Purpose of the Waiver Request:
Secondary data and tissue analyses of existing data and tissues

2. Type of Request:
Waiver of Informed Consent

a. **Will deception be used?** ○ Yes ◉ **No**

If yes, provide the rationale and describe the debriefing procedures:

3. **List the identifying information you plan to collect or keep a link to (e.g. names, dates, or identification numbers such as social security numbers or medical record numbers, etc.).**
The existing database and biorepository will have study IDs that are linked to names, dates, MRN and other PHI. Investigators will be able to view these identifiers, but will not record them in individual datasets for use in projects covered under this umbrella application.

4. **Explain why the research could not practicably be conducted without the waiver or alteration. For example, complete the following sentence "If I had to obtain consent, the research could not be conducted because...":**
If consent were a requirement, the investigator would be unable to obtain consent for about 60% of participants because they have moved and lost to follow-up and the contact information in our database in incorrect. With a loss of 60% of participants, the investigator would be unable to answer the research question.

Additionally, consent was previously given by participants for future tissue research.

5. **Explain why the research and privacy risk of the research are no more than *minimal:***
The research and privacy risk of the research are no more than minimal because the main risk is a breach of confidentiality and procedures are in place to make such breaches very unlikely.

6. **Describe the measures you will take to ensure the waiver or alteration will not adversely affect the rights and welfare of the *subjects:***
The research will not change the care the individual received

7. **Explain how you will, if applicable and appropriate, provide the subjects with additional pertinent information *after* they have participated in the study, or indicate *"Not applicable":***
Not applicable

5. Data Monitoring Plan

1. **Privacy Protections:** Privacy refers to persons and to their interest in controlling access of others to themselves. Privacy can be defined in terms of having control over the extent, timing and circumstances of sharing oneself (physically, behaviorally, or intellectually) with others. **What precautions will be used to ensure subject privacy is protected?**

Select all that apply:

The collection of information about participants is limited to the amount necessary to achieve the aims of the research, so that no unneeded information is being collected

Other or additional details (specify):

Other or additional details (specify):
Participants already completed the studies

2. **Confidentiality Precautions:** Confidentiality is an extension of the concept of privacy; it refers to the subject's understanding of, and agreement to, the ways identifiable information will be stored and shared. Identifiable information can be printed information, electronic information or visual information such as photographs. **What precautions will be used to maintain the confidentiality of identifiable information?**

Select all that apply:

Storing research data on password protected computers or in locked cabinets or offices

Complete de-identification of study data

All data that will be transferred or transported outside of the institution will be encrypted

Other or additional details (specify):

3. **Will photos, audio recordings, or video recordings, or medical images of participants be made during the study?**
○ Yes ◉ **No**

If yes, describe the recording/images and what will become of them after creation (e.g., shown at scientific meetings, stored in the medical/research record, transcribed, erased, etc.):

4. **How will study data and documentation be monitored throughout the study?**

Select all that apply:

Other or additional details (specify):

Other additional details (specify):

The study team will maintain a record of all specific projects and analyses that are conducted under this protocol, including documentation that each is conducted in accordance with the procedures and provisions described in this umbrella application. A report of the specific, individual projects/analyses will be submitted annually to the IRB via the ERICA Report Form for acknowledgement. This report will include the name of the investigators who conducted the specific project, the date the project began and ended (if ended), the actual or estimated number of patients whose data/tissue were/will be analyzed, and a short description of the specific aims and procedures for the projects.

The PI will ensure that any substantial amendments to the umbrella protocol, including changes in co-investigators, will be submitted to the IRB via an amendment application.

The PI will also ensure that all possible unanticipated problems or instances of non-compliance related to any individual projects under this umbrella will be reported to the IRB according to standard IRB reporting policies.

5. Who will be the primary monitor of the study data and documentation?

Select all that apply:

Principal Investigator

Study Coordinator or Research Nurse

Other or additional details (specify):

6. How often is study data and documentation monitoring planned (e.g., monthly, twice a year, annually, after N participants are enrolled, etc.)?
Annually

6. Risks and Benefits

1. Describe the reasonable foreseeable risks or discomforts to the participants:

The risk is breach of confidentiality. The study procedures will minimize the risk.

2. Describe the potential benefits to society AND to participants (do not include compensation):

Understanding cardiovascular disease and nutritional issues in CKD will be of benefit to the society. There are no direct benefits to participants.

3. Are there any costs to the participants from participation in research?

○ Yes ◉ **No**

If yes, specify:

4. Is there any compensation to the participants?

○ Yes ◉ **No**

a. If yes, answer the following:
Specify overall amount:

b. Specify when participants will be paid (e.g. at each visit, at end of study, etc.):

c. If applicable, please specify payment by visit or other time interval (e.g. $10 per visit, etc.):

d. If applicable, explain plan for prorating payments if participant does not complete the study:

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7. HIPAA and the Covered Entity

1. Does this study involve Protected Health Information (PHI) or de-identified health information?

◉ **Yes** ○ No

a. If yes, select the method(s) of authorization that will be used:
Waiver or Alteration of Authorization

If needed, select De-Identification Form:

b. If yes, will PHI be disclosed outside the Covered Entity?
○ Yes ◉ **No**

If so, to whom?

And for what purposes?

2. Does this study involve any of the following:

a. The investigational use of a drug?
○ Yes ◉ **No**

b. The investigational use of a medical device?
○ Yes ◉ **No**

c. Is this an investigator-initiated drug or device trial lead by the Principal Investigator?
○ Yes ◉ **No**

d. Exposure to radioisotopes or ionizing radiation?
○ Yes ◉ **No**

e. Does the study involve cancer patients and/or address a cancer question?
○ Yes ◉ **No**

f. Obtaining data or information from the UUHSC Enterprise Data Warehouse (EDW) in a query outside of the Utah Population Database (UPDB)?
○ Yes ◉ **No**

g. Any component of the Center for Clinical and Translational Science (CCTS)?
◉ **Yes** ○ No

The Clinical Services Core (CSC)?
○ Yes ◉ **No**

h. A Humanitarian Device Exemption (HDE)?
○ Yes ◉ **No**

i. Creating or sending samples to a tissue bank/repository?
○ Yes ◉ **No**

j. The use of human subjects and biological agents (e.g., staphylococcus aureus, adenovirus), or the deliberate transfer of recombinant DNA vectors/plasmids (recombinant DNA, or DNA or RNA derived from recombinant DNA) or synthetic DNA into human research participants?
○ Yes ◉ **No**

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Request for Waiver or Alteration of Authorization

Request for Waiver of Authorization for Recruitment Only
This option must only be used if you are reviewing PHI in order to identify eligible participants BEFORE approaching them to obtain consent and authorization. All other waiver requests must be entered below.

Other Requests for Waivers of Authorization:

- *Click "Add" below to add a new waiver request to this application.*
- *Click the waiver name link to edit a waiver that has already been created.*
- *To delete a waiver request, contact the IRB.*

	Date Created	Type of Request	Purpose of Waiver Request
View	7/1/2014	Waiver of Authorization	Secondary data and tissue analyses using existing data and tissues

Request for Waiver or Alteration of Authorization

1. **Purpose of the Waiver Request:**
   Secondary data and tissue analyses using existing data and tissues
2. **Type of Request:**
   Waiver of Authorization
3. **List the identifying information you plan to collect or keep a link to (e.g. names, dates, or identification numbers such as social security numbers or medical record numbers, etc).**
   The existing database and biorepository will have study IDs that are linked to names, dates, MRN and other PHI. Investigators will be able to view these identifiers, but will not record them in individual datasets for use in projects covered under this umbrella application.
4. **Explain why the *PHI* to be used or disclosed is the minimum necessary to accomplish the research objectives:**
   Investigators will only record the data points necessary for their individual analysis project and will not record identifiers.
5. **Explain why the research could not practicably be conducted without the waiver of authorization.** *For example, complete the following sentence: "If I had to obtain authorization, the research could not be conducted because..."*
   If consent and authorization were a requirement, the investigator would be unable to obtain consent and authorization for about 60% of participants because they have moved and lost to follow-up and the contact information in our database in incorrect. With a loss of 60% of participants, the investigator would be unable to answer the research question.

   Additionally, consent and authorization was previously given by participants for future tissue research.
6. **Describe your plan to protect the identifiers from improper use and disclosure, and indicate where the *PHI* will be stored and who will have access:**
   Identifiers will not be recorded or retained in the individual datasets.
7. **The identifiers must be destroyed at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law. Describe how and when you will destroy the identifiers, or justify their retention:**
   Identifiers will not be recorded or retained in the individual datasets.
8. **Describe the measures you will take to ensure the PHI will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research approved by the IRB:**
   Investigators will not disclose identifiable information outside of the covered entity because they will not be collecting or recording identifiers.

8. Resources and Responsibilities

1. **State and justify the qualifications of the study staff:**

   Study Coordinator and research assistant with experience in research and HIPPA and CITI certified.
2. **Describe the training that study staff and investigators will receive in order to be informed about the protocol and understand their research-related duties and functions:**

   Monthly meetings to review study progress and activities.

   All staff will be trained on how to use this umbrella protocol according to IRB guidelines with explanation of rational for the study. They will

compile the required research training and maintain certificates. HIPPA training will be maintained to ensure the privacy of the research patients. Some of these trainings are done online and will be monitored to ensure timely compilation of the training.

3. **Describe the facilities to be used for the research activities (e.g. hospitals, clinics, laboratories, classrooms/schools, offices, tissue banks, etc.):**
   We are only performing data analysis. Thus all research activities will be completed in our research offices.

4. **Describe the medical or psychological resources available at this site (and other participating sites, if applicable) that participants might require as a consequence of the research. If not applicable, please state.**
   We are only performing data analysis. All data collection has already been complete; participants are no longer undergoing study intervention and thus do not require medical or psychological resources.

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Documents and Attachments

If any of your documents (such as investigational brochures, sponsor protocols, advertisements, etc.) are not available in an electronic format, please scan and save them as PDF files or contact our office for assistance.

Naming Documents: Please use the title field to clearly indicate the content of each form. The name you enter will be listed on your approval letter. Use names that will differentiate from earlier versions.

Examples:
Consent Document Control Group 04/14/05
Consent Document Treatment Group 4/14/05
Sponsor Protocol 04/14/05 Version 2
Assent Document (Highlighted Changes)

Apple/Macintosh Users: MS Word documents must have a .doc file extension. See ERICA home page for instructions.

Print View: IRB Draft Protocol Summary

eProtocol Summary:

Name	Version	Date Created	Date Modified
There are no items to display			

Consent Documents, Consent Cover Letters, Consent Information Sheets, Consent Scripts, etc.:

Name	Version	Date Created	Date Modified
There are no items to display			

Parental Permission Documents:

Name	Version	Date Created	Date Modified
There are no items to display			

Assent Documents:

Name	Version	Date Created	Date Modified
There are no items to display			

VA Consent Documents:

Name	Version	Date Created	Date Modified
There are no items to display			

Surveys, Questionnaires, Interview Scripts, etc.:

Name	Version	Date Created	Date Modified

There are no items to display

Full Protocol (company protocol, sponsor protocol, investigator-initiated protocol, etc.):

Name	Version	Date Created	Date Modified

There are no items to display

Investigational Brochure (IB) for Investigational Drug or Drug/Device Package Insert:

Name	Version	Date Created	Date Modified

There are no items to display

Grant Application:

Name	Version	Date Created	Date Modified

There are no items to display

Literature Cited/References:

Name	Version	Date Created	Date Modified

There are no items to display

Principal Investigator's Scholarly Record (CV/Resume):

Name	Version	Date Created	Date Modified

There are no items to display

Faculty Sponsor's Scholarly Record (CV/Resume):

Name	Version	Date Created	Date Modified

There are no items to display

Other Stamped Documents:

Only attach documents here as directed by the IRB, such as the Data/Information Request Form for UUHSC EDW.

Name	Version	Date Created	Date Modified

There are no items to display

Recruitment Materials, Advertisements, etc.:

Name	Version	Date Created	Date Modified

There are no items to display

Other Documents:

Name	Version	Date Created	Date Modified

There are no items to display

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Finish Instructions

Finish Instructions

1. **To view errors, select the "Hide/Show Errors" option at the top or bottom of the page. If you have errors on your application, you won't be able to submit it to the IRB.**
2. **Selecting the Finish button will NOT submit the application to the IRB.**
   You MUST select the "Submit" option on the workspace once you've selected the "Finish" button.
3. **If your study has a faculty sponsor: Once the PI submits the application, it will be sent to the faculty sponsor for final approval. The IRB cannot review the study until the faculty sponsor submits the application to the IRB.**