Human Subjects Protocol (HSP)

Form Version: October 15, 2008

- **You are applying** for IRB review of the research described in this form.
- **To avoid delay**, respond to all items in order and include all required approvals and documents.
- **To complete the form**, click the underlined areas and type or paste in your text; double-click checkboxes to check/uncheck. For more tips, see www.uab.edu/irb/forms.
- **Mail or deliver all materials to AB 470**, 701 20th Street South, Birmingham, AL 35294-0104.

Indicate the type of review you are applying for:

☒ Convened (Full) IRB *or*

☐ Expedited—See the Expedited Category Review Sheet, and indicate the category(ies) here: ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7

1. IRB Protocol Title: Vascular Effects of Mineralocorticoid Receptor Antagonism in Kidney Disease

2. Investigator, Contacts, Supervisors

a. Name of Principal Investigator: **Eric Judd**

Degree(s)/Title: **MD/Instructor** BlazerID: **ejudd**

Dept/Div: **Medicine/Nephrology** Mailing Address: **Paula, Rm 223** UAB ZIP: **0007**

Phone: **975-9676** Fax: **975-8879** E-mail: **ejudd@uab.edu**

b. Name of Contact Person: **Felice Cook** Title: **Program Coordinator II** Phone: **4-1400**

E-mail: **fycook@uab.edu** Fax: **4-1302**

Mailing Address (if different from that of PI, above): **CH19, Room 115**

INVESTIGATOR ASSURANCE STATEMENT & SIGNATURE

By my signature as Principal Investigator, I acknowledge my responsibilities for this Human Subjects Protocol, including:

- Certifying that I and any Co-Investigators or Other Investigators comply with reporting requirements of the UAB Conflict of Interest Review Board;
- Certifying that the information, data, and/or specimens collected for the research will be used, disclosed and maintained in accordance with this protocol and UAB policies;
- Following this protocol without modification unless (a) the IRB has approved changes prior to implementation or (b) it is necessary to eliminate an apparent, immediate hazard to a participant(s);
- Verifying that all key personnel listed in the protocol and persons obtaining informed consent have completed initial IRB training and will complete continuing IRB training each year;
- Verifying that all personnel are licensed/credentialed for the procedures they will be performing, if applicable;
- Certifying that I and all key personnel have read the *UAB Policy/Procedure to Ensure Prompt Reporting of Unanticipated Problems Involving Risks to Subjects or Others to the IRB, Institutional Officials, and Regulatory Agencies* and understand the procedures for reporting;
- Applying for continuing review of the protocol at least annually unless directed by the IRB to apply more frequently;
- Conducting the protocol as represented here and in compliance with IRB determinations and all applicable local, state, and federal law and regulations; providing the IRB with all information necessary to review the protocol; refraining from protocol activities until receipt of initial and continuing formal IRB approval.

Signature of Investigator:_____ **Date:**_____

c. List all staff who will be involved with the design, conduct, and reporting of the research, their degree(s) and job title, and any additional qualifications. Include individuals who will be involved in the consent process. *Repeat the table below for each individual.*
Note. For studies involving investigational drugs, include all investigators who will be listed on FDA Form 1572 and attach a copy, if applicable. Send the IRB a copy of Form 1572 anytime you update the form with the FDA.

Role:	☒Co- *-OR-* ☐Other *–AND/OR-* ☒Consent Process
Full Name:	**Eric Judd**
Primary UAB Dept.:	**Medicine**
(Employer if not UAB)	
Degree(s) / Job Title:	**M.D./ Instructor**
Additional Qualifications pertinent to the study:	____

Role:	☒Co- -OR- ☐Other –AND/OR- ☒Consent Process
Full Name:	**David A. Calhoun**
Primary UAB Dept.:	**Medicine**
(Employer if not UAB)	
Degree(s) / Job Title:	**M.D./Professor**
Additional Qualifications pertinent to the study:	____

Role:	☒Co- -OR- ☐Other –AND/OR- ☒Consent Process
Full Name:	**Michael Allon**
Primary UAB Dept.:	**Medicine**
(Employer if not UAB)	
Degree(s) / Job Title:	**M.D./Professor**
Additional Qualifications pertinent to the study:	____

Role:	☒Co- -OR- ☐Other –AND/OR- ☒Consent Process
Full Name:	**Tanja Dudenbostel**
Primary UAB Dept.:	**Medicine**
(Employer if not UAB)	
Degree(s) / Job Title:	**M.D./Assistant Professor**
Additional Qualifications pertinent to the study:	____
Additional Qualifications pertinent to the study:	____

Role:	☒Co- -OR- ☐Other –AND/OR- ☒Consent Process
Full Name:	**Mohammed Siddiqui**
Primary UAB Dept.:	**Medicine**
(Employer if not UAB)	
Degree(s) / Job Title:	**M.D./Postdoctoral Fellow**
Additional Qualifications pertinent to the study:	____

Role: ☒Co- -OR- ☐Other –AND/OR- ☐Consent Process
Full Name: **Gary Cutter**
Primary UAB Dept.: **Biostatistics**
(Employer if not UAB)
Degree(s) / Job Title: **Ph.D./Professor**
Additional Qualifications pertinent to the study: ____

Role: ☒Co- -OR- ☐Other –AND/OR- ☐Consent Process
Full Name: **Rakesh Patel**
Primary UAB Dept.: **Molecular & Cellular Pathology**
(Employer if not UAB)
Degree(s) / Job Title: **Ph.D./Professor**
Additional Qualifications pertinent to the study: ____

Role: ☒Co- -OR- ☐Other –AND/OR- ☐Consent Process
Full Name: **Salam Madi**
Primary UAB Dept.: **Medicine**
(Employer if not UAB)
Degree(s) / Job Title: **MSc/Research Coordinator**
Additional Qualifications pertinent to the study: ____

d. Is the principal investigator a student, fellow, or resident? ☐Yes ☒No
If Yes, complete items below and obtain signature of faculty advisor or supervisor:
Supervisor's Name:
Degree(s) / Job Title:
Additional Qualifications pertinent to the study:
Telephone:
E-Mail:
Signature: _____

e. Describe the principal investigator's activities related to this protocol and provisions made by the PI to devote sufficient time to conduct the protocol:
This clinical trial constitutes the primary project for Dr. Judd's career development award, for which he will receive 80% dedicated research time for 5 years. Dr. Judd will oversee all aspects of the study including the consent process, vascular function testing, biochemical specimen collection and storage, study visits, dispensing of study medication, data storage, and data analysis.

f. Is medical supervision required for this research? ☒Yes ☐No
If Yes, who will provide the supervision?
☒ PI will provide -*OR*- Name:_____Telephone:
If other than PI, obtain signature of person providing medical supervision:
Signature _____

g. Describe the process that ensures that all persons assisting with the research are adequately informed about the protocol and their research-related duties and functions: **The co-investigators contributed to the design of the proposed protocol. The protocol roles of all study personnel will be reviewed prior to study initiation, annually and with any change(s) in protocol.**

3. Funding

Is this study funded? ☒Yes ☐No

If No, specify that costs of the study will be covered by funds from the UAB department or other source named:

If Yes, attach one copy of completed application or request for funding sent to sponsor, and complete a-d.

a. Title of Grant or Contract: **Vascular effects of mineralocoriticoid receptor antagonism in kidney disease**

b. PI of Grant or Contract: **Eric Judd**

c. Office of Grants & Contracts Administration Link or Tracking Number: **Pending**
(*or enter "Pending" and provide upon receipt from OGCA*)

d. Sponsor, Funding Route (*check and describe all that apply*):

- ☒ Gov't Agency or Agencies—Agency name(s): National Institutes of Health
- ☐ NIH Coop. Group Trial—Group name:____
- ☐ Private Nonprofit (e.g., Foundation)—Name:____
- ☐ Industry, investigator-initiated—Name:____ Describe the funding arrangement:____
  Note. Western IRB reviews industry-sponsored protocols unless the investigator initiated the research, or the study qualifies for expedited review or involves gene therapy.
- ☐ UAB Departmental/Division Funds—Specify:

4. Conflict of Interest—Human subjects research involving a disclosed financial interest is subject to IRB review following review by the Conflict of Interest Review Board.

The following definitions are used for Item #4:

Immediate family means spouse or a dependent of the employee. *Dependent* is any person, regardless of his or her legal residence or domicile, who receives 50% or more of his or her support from the public official or public employee or his or her spouse or who resided with the public official or public employee for more than 180 days during the reporting period.

Financial Interest Related to the Research means financial interest in the sponsor, product or service being tested, or competitor of the sponsor.

For each investigator and staff member who are involved in the design, conduct and reporting of the research (2a. and c.) answer the questions below: **(Repeat the section below for each individual)**

Name: **Eric Judd**

Do you or your immediate family have any of the following? (check all that apply)

- ☐ An ownership interest, stock options, or other equity interest related to the research of any value.

- ☐ Compensation related to the research unless it meets two tests:
  - Less than $10,000 in the past year when aggregated for the immediate family.
  - Amount will not be affected by the outcome of the research.
- ☐ Proprietary interest related to the research including, but not limited to, a patent, trademark, copyright, or licensing agreement.
- ☐ Board of executive relationship related to the research, regardless of compensation.

Name: **David A. Calhoun**

Do you or your immediate family have any of the following? (check all that apply)

- ☐ An ownership interest, stock options, or other equity interest related to the research of any value.
- ☐ Compensation related to the research unless it meets two tests:
  - Less than $10,000 in the past year when aggregated for the immediate family.
  - Amount will not be affected by the outcome of the research.
- ☐ Proprietary interest related to the research including, but not limited to, a patent, trademark, copyright, or licensing agreement.
- ☐ Board of executive relationship related to the research, regardless of compensation.

Name: **Michael Allon**

Do you or your immediate family have any of the following? (check all that apply)

- ☐ An ownership interest, stock options, or other equity interest related to the research of any value.
- ☐ Compensation related to the research unless it meets two tests:
  - Less than $10,000 in the past year when aggregated for the immediate family.
  - Amount will not be affected by the outcome of the research.
- ☐ Proprietary interest related to the research including, but not limited to, a patent, trademark, copyright, or licensing agreement.
- ☐ Board of executive relationship related to the research, regardless of compensation.

Name: **Tanja Dudenbostel**

Do you or your immediate family have any of the following? (check all that apply)

- ☐ An ownership interest, stock options, or other equity interest related to the research of any value.
- ☐ Compensation related to the research unless it meets two tests:
  - Less than $10,000 in the past year when aggregated for the immediate family.
  - Amount will not be affected by the outcome of the research.
- ☐ Proprietary interest related to the research including, but not limited to, a patent, trademark, copyright, or licensing agreement.
- ☐ Board of executive relationship related to the research, regardless of compensation.

Name: **Salam Madi**

Do you or your immediate family have any of the following? (check all that apply)

- ☐ An ownership interest, stock options, or other equity interest related to the research of any value.
- ☐ Compensation related to the research unless it meets two tests:
  - Less than $10,000 in the past year when aggregated for the immediate family.
  - Amount will not be affected by the outcome of the research.
- ☐ Proprietary interest related to the research including, but not limited to, a patent, trademark, copyright, or licensing agreement.
- ☐ Board of executive relationship related to the research, regardless of compensation.

Name: **Mohammed Siddiqui**

Do you or your immediate family have any of the following? (check all that apply)

- ☐ An ownership interest, stock options, or other equity interest related to the research of any value.
- ☐ Compensation related to the research unless it meets two tests:
  - Less than $10,000 in the past year when aggregated for the immediate family.
  - Amount will not be affected by the outcome of the research.
- ☐ Proprietary interest related to the research including, but not limited to, a patent, trademark, copyright, or licensing agreement.
- ☐ Board of executive relationship related to the research, regardless of compensation.

Name: **Gary Cutter**

Do you or your immediate family have any of the following? (check all that apply)

- ☐ An ownership interest, stock options, or other equity interest related to the research of any value.
- ☐ Compensation related to the research unless it meets two tests:
  - Less than $10,000 in the past year when aggregated for the immediate family.
  - Amount will not be affected by the outcome of the research.
- ☐ Proprietary interest related to the research including, but not limited to, a patent, trademark, copyright, or licensing agreement.
- ☐ Board of executive relationship related to the research, regardless of compensation.

Name: **Rakesh Patel**

Do you or your immediate family have any of the following? (check all that apply)

- ☐ An ownership interest, stock options, or other equity interest related to the research of any value.
- ☐ Compensation related to the research unless it meets two tests:
  - Less than $10,000 in the past year when aggregated for the immediate family.
  - Amount will not be affected by the outcome of the research.
- ☐ Proprietary interest related to the research including, but not limited to, a patent, trademark, copyright, or licensing agreement.

☐ Board of executive relationship related to the research, regardless of compensation.

If you checked any of the above, a financial interest disclosure has to be submitted to or currently be on file with the CIRB. A completed CIRB Evaluation has to be available before the IRB will conduct its review.

5. Locations Involved

a. Describe the facilities available for the conduct of the research. For research on UAB campus, include building names and room numbers: **115 Community Health Services Building; UAB Outreach Laboratory Services, O'Brien Center Bioanalytical Core**

b. Indicate all "performance sites" that will provide space, services, facilities, potential or actual participants, or other support for this protocol.

☒ The Kirklin Clinic (TKC)
☒ University of Alabama Hospital (UAHosp)
☐ The Children's Hospital of Alabama (TCHA)
☐ Callahan Eye Foundation Hospital (CEFH)
☐ UAB Highlands
☐ Jefferson County Dept. of Health (JCDH)
☐ Birmingham Veterans Affairs Medical Center (BVAMC)
☐ General Clinical Research Center (GCRC)—inpatient
☐ General Clinical Research Center (GCRC)—outpatient
☐ General Clinical Research Center (GCRC) at The Kirklin Clinic (TKC)
☒ Other (i.e., Any performance site not listed above, including those covered by subcontracts related to this protocol)—Describe: **CHSB Room 115**

c. Is this study a clinical trial requiring clinical services at one of the performance sites listed in Item b above? ☒Yes ☐No
If Yes, Fiscal Approval Process (FAP)-designated units complete a FAP submission and send to fap@uab.edu. For more on the UAB FAP, see www.uab.edu/ohr.

d. Is this a field study? ☐Yes ☒No
If Yes, describe the community:____

e. Is the study to be undertaken within a school, business, or other institution that does not have an institutional review board? ☐Yes ☒No
If Yes, attach a statement of any contacts with and approvals from the appropriate institution officials.
Note. Documentation of all such approvals must be received by the UAB OIRB before IRB approval will be issued.

f. Has this protocol or project been reviewed by another IRB, similar review board, or departmental review committee(s) that authorizes the use of its patient populations? ☐Yes ☒No
If Yes, provide name of the review board(s):____ and for each board listed, enter either the date of latest approval(s) or "PENDING":____ or reasons not approved:____. *If this protocol is subsequently rejected or disapproved by another review board, the UAB IRB must be notified promptly.*

Attach copies of approvals/disapprovals.

g. Will any of the participants be from the Birmingham Veterans Affairs Medical Center? ☐Yes ☒No
If Yes, attach VA IRB approval or notification from the VA Research and Development Department that the study has been submitted to the VA IRB for review.

h. Will the study be conducted at or recruit participants from the Jefferson County Department of Public Health (JCDH)? ☐Yes ☒No
If Yes, attach notification that the protocol has been approved by JCDH or the Alabama Department of Public Health IRB.

6. Multi-Site Studies

a. Is the investigator the lead investigator of a multi-site study? ☐Yes ☒No
b. Is UAB a coordinating site in a multi-site study? ☐Yes ☒No
c. If you answered **Yes** to *a* or *b*, describe the management of information obtained in multi-site research that might be relevant to the protection of participants. Include, at a minimum, the following items:

- IRB approvals from other sites
- Unanticipated problems involving risks to participants or others. (For example, if there is an unanticipated problem involving risks to participants or others, which site is responsible for reporting it?)
- Interim results.
- Protocol modifications.

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7. Drugs: Will any drugs or supplements be used/studied in this protocol? ☒Yes ☐No
If Yes, attach the Drug Review Sheet.

8. Devices: Will any devices be studied in this protocol or used for a purpose other than for which they were approved by the FDA? ☐Yes ☒No
If Yes, attach the Device Review Sheet.

9. Special Approvals

a. Does this project involve the use of radioisotopes? ☐Yes ☒No
If Yes, attach documentation of approval from the Radiation Safety Division.

b. Does this project include patients with contagious infections (e.g., mumps, measles, chickenpox, TB, meningitis)? ☐Yes ☒No
If Yes, attach documentation of approval from Chairman of the Infection Control Committee of the appropriate facilities.

c. Does this project involve obtaining remnant biopsy or surgical material from the Department of Pathology or any other source? ☐Yes ☒No
If Yes, attach documentation of approval from the entity or individual providing the materials (e.g., the UAB Division of Anatomic Pathology Release of Pathologic Materials).

d. Does this project require obtaining any remnant clinical laboratory specimens, body fluids, or microbiological isolates from the Department of Pathology or any other source? ☐Yes ☒No

If Yes, attach documentation of approval from the entity or individual providing the materials (e.g., the UAB Division of Laboratory Medicine Release of Pathologic Materials).

e. Does this project use stored (existing) specimens from a repository? ☐Yes ☒No
If Yes, attach documentation of approval for use of specimens, and describe how existing specimens are labeled:____

10. Use of Specimens

Does this project involve collecting specimens from participants and storing them for future research? ☒Yes ☐No

If Yes, complete a-h. If no, skip to Item 11

a. How will specimens be obtained, processed, distributed, and stored?
Blood and urine from 3 study visits will be labeled and stored in a Fisherbrand cryo/freezer box in a temperature controlled and monitored freezer located in the Ziegler Research Building (Rm 510)

b. How will specimens be labeled (e.g., unique identifier, medical record number, Social Security number, name, date of birth)?
Specimens will be labeled by study name, participant study number, and date of collection.

c. How will clinical data associated with the specimens be collected and stored?
Clinical data associated with the specimens will be kept in the study database. The database will be maintained on a computer with access restricted by password protection to study staff. A non-specific participant number will be generated for each participant. The list linking the participant numbers to the participant identifiers will kept in a secure location with password-protection and only the PI and designated study personnel will have access to this list. Data will be stored with use of the participant numbers without identifiable labels such as names, medical record number or social security number.

d. What participant-identifying information will be collected and linked to the specimens?
Participant name and date of birth will be recorded in the list linking participant number to the participant identifiers.

e. What steps will be taken to maximize the confidentiality of linked identifiers? For example, procedures could include using a password-protected computer database to link identifiers, with limited personnel knowledgeable of the password, or coded identifiers released without the ability to link to clinical data (also called "stripped" or "anonymized" specimens).
As described in part c, data collected throughout the study will be stored in a database maintained on a computer with access restricted by password protection to study staff. The specimens will be labeled with de-identified codes (participant number and date of collection).

f. Will specimens be shared with other investigators in the future? ☒Yes ☐No
If Yes, what identifiers, clinical information and demographic information will be shared; or will the specimens be stripped of identifiers (i.e., anonymized)? Also **if yes**, outline your procedure for assuring IRB approval for release and use prior to release of specimens.
Specimens that are provided to other investigators will remain stripped of identifiers. Participant demographics including age, gender, race, and comorbidities will also be provided in a de-identified form using participant study number (e.g., CKD1501).

Note. Investigators who receive and/or use these specimens must document approval from the appropriate IRB(s) before the specimens may be released.

g. Will biological samples be stored for future use? ☒Yes ☐No
If Yes, indicate whether they will be used for the disease under study in this protocol or research on other diseases.
Blood and urine samples will be stored with the potential for future testing for the disease under this study protocol (e.g., vascular function in chronic kidney disease).

h. Is genetic testing planned? ☒Yes ☐No
If Yes, describe the planned testing here and see "DNA/Genetic Testing" in the Guidebook for consent requirements.
Cells from the blood sample will be stored for the potential to test for specific genetic variations (i.e., polymorphisms that alter the response to spironolactone).

11. Gene Therapy

Does this project involve gene therapy or administering recombinant materials to humans? ☐Yes ☒No

If Yes, submit the Gene Therapy Project Review Panel Report –OR- If this is a vaccine trial that is exempt from the NIH Guidelines For Research Involving Recombinant DNA Molecules, submit the Protocol Oversight Review Form For Clinical Vaccine Trials.

12. HIPAA Privacy and Security

Will the PI or others obtain, review, or make other use of participants' "personal health information" (i.e., information, whether oral or recorded in any form or medium that (a) is created or received by a health care provider and (b) relates to past, present, or future physical or mental health or condition of an individual; or provision of health care; or payment for provision of heath care)? ☒Yes ☐No

If Yes, complete a-e as described.

a. Will the data/information be stored or managed electronically (on a computer)? ☒Yes ☐No

b. Is the principal investigator requesting that the UAB IRB waive patient HIPAA authorization from another institution or entity (e.g., insurance company, collaborating institution). ☐Yes ☒No
If Yes, attach copy of privacy notices from institution/entity, and provide the name of institution/entity:____

c. Indicate which, if any, of the listed entities below would provide information or maintain health information collected for this protocol and/or where health information that been collected will be stored/maintained.
☒ The Kirklin Clinic
☒ University of Alabama Hospital
☐ The Children's Hospital of Alabama
☐ Callahan Eye Foundation Hospital
☐ UAB Highlands
☐ Jefferson County Department of Health
☐ School of Dentistry

☐ School of Health Professions
☐ School of Medicine
☐ School of Nursing
☐ School of Optometry
☐ University of Alabama Health Services Foundation
☐ UAB Health Centers
☐ Viva Health
☐ Ophthalmology Services Foundation
☐ Valley Foundation
☐ Medical West - UAB Health System Affiliate

Health System Information Systems:

☐ HealthQuest
☐ Cerner Millennium (Lab, Radiology, UED, Surgery)
☐ EMMI - Master Member Index
☒ Horizon - IPV (IVR/CDA/CRIS)
☐ CareFlow Net
☐ Eclipsys (PIN)
☒ IMPACT
☐ None—**If None, skip to Item 13.**

d. Indicate which of the listed identifiers would be associated/linked with the protected health information (PHI) used for this protocol.

☒ Names
☒ Geographic subdivisions smaller than a State
☒ Elements of dates (except year) related to an individual
☒ Telephone numbers
☐ Fax numbers
☐ Email addresses
☐ Social security numbers
☒ Medical record numbers
☐ Health plan beneficiary numbers
☐ Account numbers
☐ Certificate/license numbers
☐ Vehicle identifiers and serial numbers
☐ Device identifiers and serial numbers
☐ Biometric identifiers
☐ Web universal resource locators (URLs)
☐ Internet protocol address numbers
☐ Full-face photographic images
☐ Any other unique identifying number—Describe:____

Note. Codes are not identifying as long as the researcher cannot link the data to an individual

☐ None—**If None, skip to Item 13.**

e. Choose one plan to describe your use of the personal health information:

☐ The data collected meet the specifications for a "limited data set"
—Attach Data Use Agreement or Business Associate Agreement

☒ Research staff will obtain authorization from each patient to use the information

—Attach Patient Authorization form, complete except for patient name and IRB protocol number

☐ PI requests Waiver of Patient Authorization to use the information
—Attach Waiver of Authorization and Informed Consent form

PROPOSED RESEARCH

- The IRB will not accept grant applications and/or sponsor's protocols in lieu of the items as outlined below.
- Do not separate responses from items. Instead, insert your response to each item below the item, keeping the information in the order of this form.
- Number each page of the Human Subjects Protocol (i.e., Page *X* of *Y*).

13. Purpose—in nontechnical, lay language

Summarize the purpose and objectives of this protocol, including any related projects, in one short paragraph.

Few therapies exist to prevent or slow the progression of chronic kidney disease, a disease with a large public health burden. This project investigates the vasculature as a novel target for chronic kidney disease treatment.

14. Background—in nontechnical, lay language

Summarize in 2-3 paragraphs past experimental and/or clinical findings leading to the formulation of this study. Include any relevant past or current research by the Principal Investigator. For drug and device studies summarize the previous results (i.e., Phase I/II or III studies).

Chronic kidney disease, an inpairment in kidney function beyond age-expected decline, is commonly attributed to kidney damage from diabetes mellitus and/or hypertension. While the direct mechanism(s) of kidney injury resulting from these comorbidities has yet to be defined, it has been hypothesized that the vasculature is involved in kidney function. This hypothesis is supported by the evidence that the one proven therapy for chronic kidney disease, namely angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), improves vascular function.

In our study of patients with resistant hypertension, we have shown that vascular function improves with the use of spironolactone, a mineralocorticoid receptor antagonist. Spironolactone has also been shown to reduce urinary protein loss in patients with chronic kidney disease. Therefore, it is reasonable to suppose that spironolactone can improve vascular function in patients with chronic kidney disease. Currently spironolactone is used sparingly in early stages of chronic kidney disease and is avoided in late stages of chronic kidney disease due to the risk of raising serum potassium levels. If spironolactone improves vascular function in patients with moderate stages of chronic kidney disease, as it has been shown to do in patients with resistant hypertension, then defining this mechanism would open new therapeutic avenues for patients with chronic kidney disease.

15. Participants (Screening and Selection)

a. How many participants are to be enrolled at UAB? **62**
If multi-center study, total number at all centers:____

b. Sex: **50% Male**
Race/Ethnicity: All races and ethnicities in the Birmingham area will be enrolled. Enrollment is expected to be composed of **65% African American (chronic kidney disease is more prevalent among African Americans).**

Age: **19-65 years of age**
Health status: **Participants with a moderate stage of chronic kidney disease**

Note. If data from prior studies indicate differences between the genders or among racial/ethnic groups in the proposed research or if there are no data to support or to negate such differences, Phase 3 clinical trials will be required to include sufficient and appropriate entry of gender and racial/ethnic subgroups so that trends detected in the affected subgroups can be analyzed. If ethnic, racial, and gender estimates are not included in the protocol, a clear rationale must be provided for exclusion of this information. If prior evidence indicates that the results will not show gender or racial differences, researchers are not required to use gender or race/ethnicity as selection criteria for study participants. They are, however, encouraged to include these groups. See Section II. Policy of the NIH POLICY AND GUIDELINES ON THE INCLUSION OF WOMEN AND MINORITIES AS SUBJECTS IN CLINICAL RESEARCH – Amended, October, 2001) for further details.

c. From what population(s) will the participants be derived?

Participants will be primarily recruited from a database of former and active patients of the UAB Hypertension Clinic totaling over 1400 patients, over 200 of which have eGFRs < 60 mL/min/1.73m^2. Additional recruitment will come from a database of patients seen in the CKD clinic at the Kirklin clinic and the PI's renal clinics both at the Kirklin Clinic and at Cooper Green.

Describe your ability to obtain access to the proposed population that will allow recruitment of the necessary number of participants:

The PI has maintained a database of hypertension patients while working in Dr. David Calhoun's Hypertension Clinic at the Kirklin Clinic. A letter signed by Dr. David Calhoun and Dr. Eric Judd will be mailed to potential participants identified in this database. The PI will recruit directly from his clinics at the Kirklin Clinic and at Cooper Green, where he is an attending in the renal clinic. A letter signed by Dr. Eric Judd and Dana Rizk, the director of the CKD clinic at the Kirklin Clinic, will be mailed to potential participants identified in the CKD database.

Describe the inclusion/exclusion criteria:

Table 1. Study inclusion and exclusion criteria	
Inclusion Criteria	• Adults (19-65 years of age) • CKD (eGFR 25-60 mL/min/1.73m^2) with urine ACR > 30 mg/gCKD (eGFR > 60 mL/min/1.73m^2) with urine ACR ≥ 300 mg/g
Exclusion Criteria	• Severe HTN (office BP ≥ 160/100 mm Hg) • Hypotension (office BP < 110/70 mm Hg) • Serum potassium > 5 mEq/L • History of arrhythmia, including atrial fibrillation • Pregnant or breast feeding woman • DM type 1 • DM type 2 with hemoglobin A1C ≥ 6.5 % • Dementia or cognitive impairment prohibiting informed consent • History of ischemic stroke, unstable angina, or myocardial infarction within the past 6 months • Allergy or intolerance to spironolactone or amiloride • Use of an MR antagonist or an epithelial sodium channel blocking medication within the last month

	• Known primary aldosteronism or renal artery stenosis

ACR = albumin-to-creatinine ratio, HTN = hypertension, BP = blood pressure, DM = diabetes mellitus, MR = mineralocorticoid receptor

Patients with severe hypertension (office BP > 160/100 mm Hg) are excluded due to 1) the possibility of requiring blood pressure medication changes during the study period, 2) direct effects of blood pressure on vascular function testing, and 3) increased cardiovascular risk leading to potential serious adverse events. Patients with hypotension (office BP < 110/70 mm Hg) were excluded due to an expected drop in blood pressure with administration of spironolactone and/or amiloride.

d. If participants will comprise more than one group or stratification, describe each group (e.g., treatment/intervention, placebo, controls, sham treatment) **and** provide the number of participants anticipated in each group.
This clinical trial follows a cross-over design. All participants are scheduled to receive both study medications in series with randomization to the initiating therapy (See Figure 2).

e. Indicate which, if any, of the special populations listed below will be involved in the protocol. Include the Special Populations Review Form (SPRF) if indicated.

- ☐ Pregnant Women: Attach SPRF—Pregnant Women, Fetuses, Neonates/Nonviable Neonates
- ☐ Fetuses: Attach SPRF—Pregnant Women, Fetuses, Neonates/Nonviable Neonates
- ☐ Neonates/Nonviable Neonates: SPRF—Pregnant Women, Fetuses, Neonates/Nonviable Neonates
- ☐ Prisoners: Attach SPRF—Prisoners
- ☐ Minors (<19 years old): Attach SPRF—Minors
- ☐ Employees or students at institution where research conducted
- ☐ Persons who are temporarily decisionally impaired
- ☐ Persons who are permanently decisionally impaired (e.g., mentally retarded)
- ☐ Non-English Speakers

For each box checked, describe why the group is included **and** the additional protections provided to protect the rights and welfare of these participants who are vulnerable to coercion:____

f. List any persons other than those directly involved in the study who will be at risk. If none, enter "None": **None**

g. Describe the process (e.g., recruitment, chart review) that will be used to seek potential participants (e.g., individuals, records, specimens). Research recruitment by non-treating physicians/staff may require completion of Partial Waiver of

Authorization for Recruitment/Screening. (See http://main.uab.edu/show.asp?durki=61981.)

For patients identified as potential participants through the hypertension and CKD databases, study personnel will review the medical history including the medical record in order to identify exclusion criteria. Eligible participants who meet inclusion and exclusion criteria after this screening process will be mailed a letter co-signed by Drs. Judd and Calhoun for the HTN database and Drs. Judd and Rizk (Dr. Dana Rizk is the Director of the CKD clinic at the Kirklin Clinic) for the CKD database. Potential participants will be contacted by phone to set up a screening visit where an investigator will review the risks and benefits of participation in a formal consenting process.

Patients recruited from the PI's Kirklin Clinic or Cooper Green clinic will have the study and its associated risks and benefits introduced by the PI during a regularly scheduled follow-up visit. Patients interested in participating will have a screening visit scheduled where informed consent will occur.

Patients who are scheduled to see a nephrologist at the Kirklin clinic will be prescreened using chart review in Impact to assess eligibility. With approval from the patient's nephrologist, patients who are eligible will be contacted either by phone or in person at their clinic visit. If interested, potential participants will be scheduled for a screening visit where the informed consent process takes place. As part of the consenting process participants are presented with a copy of the informed consent and are allowed an unlimited amount of time before deciding to proceed with the study.

In order to meet recruitment goals, the electronic health record system for University of Alabama Hospital and Kirklin Clinic will be screened using i2b2 in order to generate a list of potential study candidates. Once this list has been truncated further by chart review, the primary care doctor and/or primary nephrologist at UAB will be contacted to approve sending the patient a letter in the mail. The recruitment letter is attached.

h. If you will use recruitment materials (e.g., advertisements, flyers, letters) to reach potential participants, attach a copy of each item. If not, identify the source (e.g., databases) from which you will recruit participants. **Eligible participants identified in the hypertension and CKD databases will receive a letter alerting them to future contact by study personnel. Other participants will be recruited directly from the PI (Dr. Eric Judd's) Kirklin Clinic and Cooper Green clinic. Flyers will be posted in designated areas at Cooper Green, UAB campus, and the Kirklin Clinic.**

i. Describe the procedures for screening potential participants.

The medical history will be reviewed with the potential participant in a standard of care clinic visit. If the patient agrees to participate, an investigator will review the consent form in person with the volunteer during a screening visit. For potential participants identified in the databases, their medical records will be obtained through Horizon or Impact in order to identify exclusion criteria. Review of medical records will be limited to study personnel (either the PI, sub-investigator, or study coordinator).

16. Protocol Procedures, Methods, and Duration of the Study—in nontechnical language

a. Describe the study methodology that will affect the participants—particularly in regard to any inconvenience, danger, or discomfort.

Study participants with proteinuric, CKD will be randomly assigned in a double-masked fashion to spironolactone 25mg daily or amiloride 5 mg daily for 6 weeks and then crossed over to the alternate study medication after a 1 month wash-out period (See Figure 1). Vascular function will be assessed at baseline and the end of each 6 week treatment period by: 1) ultrasound guided flow-mediated dilation (FMD) of the brachial artery, 2) impedence cardiography, 3) pulse-wave velocity, 4)

24 hour ambulatory blood pressure monitoring, and 5) serum and urine biomarkers. Participants will undergo a total of 7 visits over 16-18 weeks; 3 of the 7 visits will involve vascular function testing.

Pulse-wave velocity is measured non-invasively with placement of a small sensor (tonometry probe) over the carotid and femoral artery. This procedure poses no discomfort and is usually done in about 15 minutes. Impedence cardiography is also noninvasive with minimal inconvenience to the participant. It is performed by placing small electrode pads on the chest wall and neck and takes about 12 minutes. FMD is measured by assessing the change in brachial artery diameter by ultrasound. A blood pressure cuff is placed below the elbow and inflated above systolic blood pressure for 5 minutes. The cuff is then released and change in brachial artery is determined immediately afterwards for 2 minutes. The entire procedure takes about 45 minutes. Some back discomfort can occur with FMD testing as participants must lie flat for 30 minutes. Hand and arm discomfort from cuff inflation is common yet resolves immediately after cuff deflation. Collection of urine for 24 hours and wearing a blood pressure monitor for 24 hours can be disruptive to normal daily/nightly activities; however poses no danger or long-term inconvenience.

A study visit where vascular function testing is to be performed will begin at 0800 in the morning and start with a vital sign assessment including height, weight, body fat percent, and left arm automated BP measurement followed by confirmation of fasting status and a brief past medical history. Each participant will then lie supine for 10 minutes in preparation for vascular function testing. Following the pulse wave velocity, impedence cardiography, and FMD measurements, the participant will have his/her blood and urine collected for laboratory testing. Laboratory testing will include ~20 mL of blood for plasma and serum testing. Participants will return 24 hour urine samples and have a 24 hour ambulatory monitor placed. This entire visit is expected to take 2 hours.

Study visits where vascular function testing will not be performed (e.g., screening visit, visit 2, visit 4, and visit 5; see Table 2) should last 30 minutes and involve a medication assessment, vital sign check, and blood collection for serum potassium (~4 mL).

All study medication will be prepared by the UAB Research Pharmacy in matching capsules. . The order of medication dispensing will follow simple randomization using an *a priori* randomization list prepared by the research pharmacy.

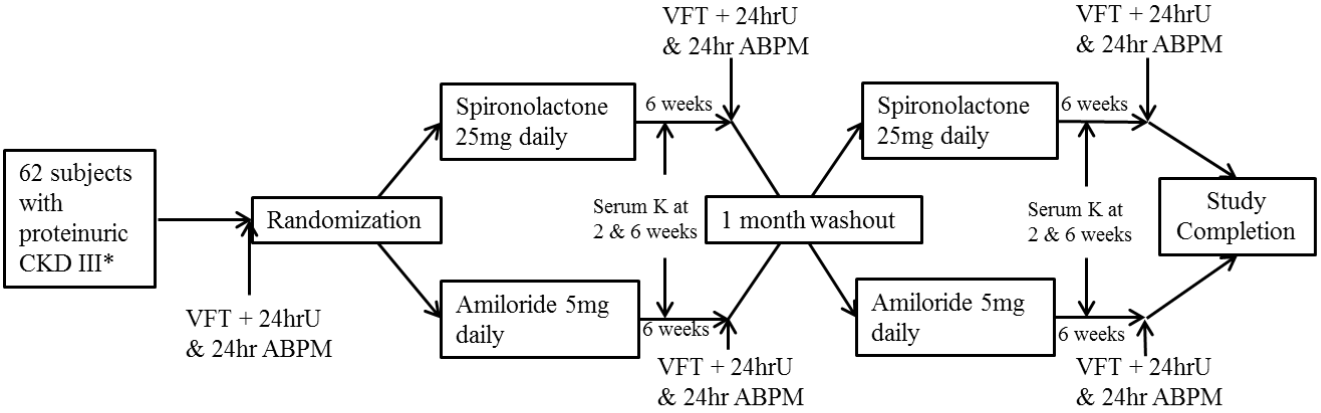

Figure 1: Study design
VFT = vascular function testing (i.e., ultrasound assessed flow-mediated dilation and biomarker measurement), 24hrU = 24 hour urine collection, 24hr ABPM = 24 hour ambulatory blood pressure monitoring, K = potassium
*30-60 mL/min/1.73m^2 eGFR by MDRD, proteinuria defined as ACR ≥ 30 mg/g

b. What is the probable length of time required for the entire study (i.e., recruitment through data analysis to study closure)?
5 years

c. What is the total amount of time each participant will be involved?
16 weeks

d. If different phases are involved, what is the duration of each phase in which the participants will be involved? If no phases are involved, enter "not applicable."
The cross-over design consists of two 6 week intervention periods separated by a one month washout period.

e. List the procedures, the length of time each will take, and the frequency of repetition, and indicate whether each is done solely for research or would already be performed for treatment or diagnostic purposes (routine care) for the population. *Insert additional table rows as needed.*

Table 2. Combined study procedure schedule

	Screen Visit Week -(1-2)	Visit 1 Week 0	Visit 2 Week 2	Visit 3 Week 6	Visit 4 Week 10	Visit 5 Week 12	Visit 6 Week 16
Informed consent	X						
Study medication pill count			X	X		X	X
Con medication assessment		X		X	X		X
Dispense study medication		X			X		
Clinic vital signs	X	X	X	X	X	X	X
FMD		X		X			X
ACR	X	X		X			X
RFP	X			X			X
24 hour ABPM		X		X			X
Plasma aldosterone, PRA		X		X			X
Blood & urine biomarkers*		X		X			X
Serum potassium via BMP			X		X	X	
24hr urine collection		X		X			X
Urine Pregnancy Test	X						

Con = concomitant, FMD = flow-mediated dilation, ACR = spot urinary albumin-to-creatinine ratio, RFP = renal function panel, PRA = plasma renin activity, BMP = basic metabolic panel, ABPM = ambulatory blood pressure monitor
*Biomarkers include serum high-sensitivity C-reactive protein (hsCRP), serum pentraxin-3 (PTX-3), serum fetuin-A, serum uric acid, plasma asymmetric dimethylarginine (ADMA), serum soluable vascular cell adhesion molecule (sVCAM-1), homeostasis model assessment method of insulin resistance (HOMA-IR), plasma and urine F2-isoprostanes, and plasma endothelin.

All procedures will be for research purposes. Study visits 1, 3, and 6 will be approximately 120 minutes in length. Study visits 2, 4, and 5 will be approximately 30 minutes in length.

f. Will an interview script or questionnaire be used? ☐Yes ☒No
If Yes, attach a copy.

g. Will participants incur any costs as a result of their participation? ☐Yes ☒No
If Yes, describe the reason for and amount of each foreseeable cost.

h. Will participants be compensated? ☒Yes ☐No
If Yes, complete i-v:
i. Type: (e.g., cash, check, gift card, merchandise): **Check**
ii. Amount or Value: **$100 for the study visits 1, 3, and 6 and $50 for study visits 2, 4, 5, screening visit, and unscheduled visit(s).**
iii. Method (e.g., mail, at visit): **Mail**
iv. Timing of Payments: (e.g., every visit, each month): **After the visit**
v. Maximum Amount of Payments per Participant: **$500 (not including any unscheduled visits)**

17. Describe the potential benefits of the research.

There is no anticipated direct benefit which the participants will obtain from participating in the protocol. However, indirect benefits may include discovering that spironolactone or amiloride reduces albuminuria and/or blood pressure. In addition, participants who experience an improvement in endothelial function with spironolactone use would be expected to have a lower cardiovascular risk with continued use. We feel the risks involved with participating in this study are reasonable in relation to the potential benefits.

18. Risks

a. List the known risks—physical, psychological, social, economic, and/or legal—that participants may encounter as a result of procedures required in this protocol. Do not list risks resulting from standard-of-care procedures. *Note. Risks included in this protocol document should be included in the written consent document.*

No undue hazards (physical, psychological, financial, legal, or other) are anticipated with vascular function testing or blood and urine sampling. Participants may be exposed to several potential risks as itemized below:

1. **Hyperkalemia: Administration of both spironolactone and amiloride are associated with increases in serum potassium of approximately 0.4 mEq/L. Serum levels of potassium will be monitored at each study visit. Kayexalate and a low potassium diet will be administered for levels of serum potassium > 5.5 meq/L followed by a repeat potassium level in 3 days. Participants will be withdrawn from the study with serum potassium levels > 6.0 meq/L. In addition, participants will not be allowed to participate in the second treatment period with a serum potassium > 5.0 meq/L when checked at week 10.**
2. **Fetal toxicity: Spironolactone is associated with fetal toxicity. Pregnant women, as determined by a screening urine sample, are excluded from study participation. Women of child bearing potential will be advised of the risk of fetal toxicity, and if a pregnancy occurs during the study the participant will be withdrawn and study medication stopped.**
3. **Gynecomastia: Spironolactone is associated with breast growth in men. This association occurs more frequently with the long-term use of doses exceeding 50mg/day.**
4. **Discomfort and risks (hematoma/skin infection) associated venous blood collection**
5. **Measurement of pulse wave velocity and performing impedence cardiography is non-invasive and entails no risk. However, measurement of FMD requires that the subject be supine for 30 minutes, and inflation of the blood pressure cuff for 5 minutes may cause discomfort.**

b. Estimate the frequency, severity, and reversibility of each risk listed.

1. **Hyperkalemia, defined as a serum potassium concentration > 5.5 mEq/L, is expected to occur in less than 5% of study participants. Serum potassium levels will be monitored within 2 weeks of starting either spironolactone or amiloride in order to prevent severe or prolonged hyperkalemia. Rises in serum potassium levels discovered in the first 2 weeks of the intervention are expected to resolve within 1-2 days of stopping the medication.**
2. **Fetal toxicity is not expected to occur during the study. Pregnant women, as determined by a screening urine sample, are excluded from study participation. If a pregnancy occurs during the study, the participant will be withdrawn and study medication stopped.**
3. **Discomfort and bruising is expected to occur in the majority of venous blood collections. However these complications of blood collection are mild. A skin infection due to blood collection is not expected to occur as standard collection techniques involving sterile materials and alcohol preparation will be employed.**

4. **Back discomfort from lying supine for 30 minutes for FMD measurement is expected to occur in less than 25% of study participants. Lumbar support pillows are available if needed. Hand and arm discomfort from blood pressure cuff inflation for 5 minutes commonly occurs with FMD measurement, yet completely resolves with cuff deflation.**

c. Is this a therapeutic study or intervention? ☒Yes ☐No

If Yes, complete the following items:

i. Describe the standard of care in the setting where the research will be conducted: **The standard of care for non-diabetic patients with moderate (stage III) CKD is control of blood pressure and avoidance of nephrotoxic agents (e.g., nonsteroidal anti-inflammatory and illicit drugs). Patients with severely, uncontrolled blood pressure (e.g., >160/100 mm Hg) will be excluded from participation.**

ii. Describe any other alternative treatments or interventions: **An angiotensin converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB) is recommended for patients who have CKD and moderate levels of albuminuria and/or uncontrolled hypertension. Participation in this clinical trial will not interfere with this therapy.**

iii. Describe any withholding of, delay in, or washout period for standard of care or alternative treatment that participants may be currently using: **Patients taking spironolactone, amiloride, or triamterene at baseline will be offered to hold this medication for 1 month prior to starting the study. All participants will undergo a 1 month washout between the 2 intervention periods.**

d. Do you foresee that participants might need additional medical or psychological resources as a result of the research procedures/interventions? ☐Yes ☒No

If Yes, describe the provisions that have been made to make these resources available.

_____

e. Do the benefits or knowledge to be gained outweigh the risks to participants? ☒Yes ☐No

If No, provide justification for performing the research:_____

19. Precautions/Minimization of Risks (If study involves drugs or devices complete the Drug or Device Review Sheet and skip to question #20)

a. Describe precautions that will be taken to avoid risks and the means for monitoring to detect risks.

b. If hazards to an individual participant occur, describe (i) the criteria that will be used to decide whether that participant should be removed from the study; (ii) the procedure for removing such participants when necessary to protect their rights and welfare; and (iii) any special procedures, precautions, or follow-up that will be used to ensure the safety of other currently enrolled participants.

c. If hazards occur that might make the risks of participation outweigh the benefits for all participants, describe (i) the criteria that will be used to stop or end the entire study and (ii) any special procedures, precautions, or follow-up that will be used to ensure the safety of currently enrolled participants.

20. Informed Consent

a. Do you plan to obtain informed consent for this protocol? ☒**Yes** ☐**No**
If Yes, complete the items below.
If No, complete and include the Waiver of Informed Consent or Waiver of Authorization and Informed Consent, as applicable.

b. Do you plan to document informed consent for this protocol? ☒**Yes** ☐**No**
If Yes, complete the items below.
If No, complete the items below **and** include the Waiver of Informed Consent Documentation.

c. How will consent be obtained? **Informed consent will be obtained by the PI or designated study personnel after reviewing the protocol, including risks, in person with the potential participant. Designated study personnel include Eric Judd (PI), Cassidy Clevenger (study coordinator), Mohammed Siddiqui (sub-investigator).**

d. Who will conduct the consent interview? **PI or designated study personnel.**

e. Who are the persons who will provide consent or permission? **Patients identified in a hypertension database from Dr. David Calhoun's Hypertension Clinic and a CKD database from Dr. Dana Rizk's CKD Clinic at the Kirklin Clinic, Dr. Eric Judd's Kirklin Clinic, Dr. Eric Judd's Cooper Green renal clinic, in the 12b2 database, or patients responding to posted flyers.**

f. What steps will be taken to minimize the possibility of coercion or undue influence?
Potential participants will be informed that they are under no obligation to participate and it will in no way affect their routine care if they elect not to enroll.

g. What language will the prospective participant or the legally authorized representative understand? **English**

h. What language will be used to obtain consent? **English**

i. If any potential participants will be, or will have been, in a stressful, painful, or drugged condition before or during the consent process, describe the precautions proposed to overcome the effect of the condition on the consent process. If not, enter "no such effect."
No such effect.

j. If any project-specific instruments will be used in the consenting process, such as flip charts or videos, describe the instrument(s) here, and provide a copy of each. If not, enter "not used."
Not used

k. How long will participants have between the time they are told about the study and the time they must decide whether to enroll? If not 24 hours or more, describe the proposed time interval and why the 24-hour minimum is neither feasible nor practical. **Potential participants are given an indefinite amount of time to make a decision. Some patients do enroll at their standard of care visits, but this is in no way obligatory.**

21. Procedures to Protect Privacy

Describe the provisions included in the research to protect the privacy interests of participants (e.g., others will not overhear your conversation with potential participants, individuals will not be publicly identified or embarrassed).

All discussions with potential participants will be done in clinic rooms with the door closed so others will not be able to overhear the conversation. Potential participants will in no way be publicly identified or embarrassed.

22. Procedures to Maintain Confidentiality

a. Describe the manner and method for storing research data and maintaining confidentiality. If data will be stored electronically anywhere other than a server maintained centrally by UAB, identify the departmental and all computer systems used to store protocol-related data, and describe how access to that data will be limited to those with a need to know.

The study database will be maintained on a computer with access restricted by password protection to study staff. A non-specific participant number will be generated for each participant (e.g., CKD1501). The list linking the participant numbers to the participant identifiers will kept in a secure location with password-protection, and only the PI and designated study personnel will have access to this list. Data will be stored with use of the participant numbers without identifiable labels such as names, medical record number or social security number.

b. Will any information derived from this study be given to any person, including the subject, or any group, including coordinating centers and sponsors? ☒Yes ☐No

If Yes, complete i-iii.

i. To whom will the information be given? **UAB IRB**

ii. What is the nature of the information? **Summary data without individual personal identifiers**

iii. How will the information be identified, coded, etc.? **Information will only be presented as summarized data without individualized information.**

23. Additional Information

In the space below, provide any additional information that you believe may help the IRB review the proposed research, or enter "None."

None