Document Coversheet

Study Title: Renin and Renal Biomarker Response to Angiotensin II Versus Controls in Septic Shock: An Open-Label Study

Institution/Site:	University of Kentucky
Document (Approval/Update) Date:	3/19/2020
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IRB Approval
3/19/2020
IRB # 57411
IRB3

PROTOCOL TYPE

Which IRB

- Medical
- NonMedical

Protocol Process Type

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

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

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

Which IRB

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

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

Which Protocol Process Type

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

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

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

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

57411

PROJECT INFORMATION

Title of Project: (If applicable, use the exact title listed in the grant/contract application). *** Effective 4/16/2020: If your research involves investigating any aspect of COVID-19, please enter "COVID19" at the start of your Project and Short Titles ***

Renin and Renal Biomarker Response to Angiotensin II Versus Controls in Septic Shock: An Open-Label Study

Short Title Description

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

Renin and Angiotensin II

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

Number of human subjects: 30

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

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

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

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

◉ Yes ○ No

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

Examples of such conditions include:

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

Attachments

Attach Type	File Name
ImpairedConsent	Form T.doc

INFORMED CONSENT/ASSENT PROCESS/WAIVER

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

Additional Resources:

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

Consent/Assent Tips:

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

How to Get the Informed Consent Section Check Mark

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

Check All That Apply

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

Attachments

Attach Type	File Name
Informed ConsentHIPAA Combined Form	Informed Consent_Clean.pdf
InformedConsent_HighlightedChanges	Informed Consent_Highlighted.docx

☐ Request for Waiver of Informed Consent Process

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

Note: The IRB does not approve waiver or alteration of the consent process for greater than minimal risk research, except

for planned emergency/acute care research as provided under FDA regulations. Contact ORI for regulations that apply to single emergency use waiver or acute care research waiver (859-257-9428).

SECTION 1.

Check the appropriate item:

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

☐ I am requesting alteration of the informed consent process.

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

SECTION 2.

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

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

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

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

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

e) If the research involves using or accessing identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format.

- Private information/specimens are “identifiable” if the investigator may ascertain the identity of the subject or if identifiers are associated with the information (e.g., medical records). This could be any of the 18 HIPAA identifiers including dates of service.
- If not using identifiable private information or identifiable biospecimens, insert N/A below.

☐ Request for Waiver of Documentation of Informed Consent Process

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

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

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

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

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

○ **Option 1**

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

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

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

○ **Option 2**

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

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

○ **Option 3**

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

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

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

RESEARCH DESCRIPTION

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

Workaround(s):

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

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

Septic shock continues to exert a large economic burden around the world. In the United States, epidemiologic data indicate a clustering effect of sepsis, and in particular, a strong clustering in the Central Appalachia region, a region served by University of Kentucky HealthCare. Several developments have occurred that lead to the current study. First, angiotensin II is the newest FDA approved vasopressor agent indicated for use in vasodilatory shock. Several subgroups from the approval trial (ATHOS-3), have indicated that angiotensin II may confer a survival benefit in certain conditions, including those patients requiring continuous renal replacement therapy, those with altered angiotensin I: angiotensin II ratios, and most recently, those with elevated renin levels (which may serve as a surrogate for dysfunctional angiotensin 1: angiotensin II ratios). Importantly, renin, angiotensin I, and angiotensin II levels are not readily available in-house.

Although angiotensin II is an FDA approved drug for vasodilatory shock, including septic shock, it was not added to the formulary at UK HealthCare and is thus not part of the current standard of care for a patient with septic shock requiring vasopressor therapy. During review at UK HealthCare ICU Committee meeting, the medication was not added to formulary due to concerns for cost, uncertainty regarding its place in therapy, and inability to restrict the drug only to sepsis patients within the healthcare enterprise.

All vasopressor therapies used in critically ill patients have a variety of side effects. Angiotensin II, when the trial data was reviewed by the FDA, was determined to have a higher rate of thrombotic risk compared to placebo, and thus was labeled with a warning regarding this high rate of thrombotic and thromboembolic risk (13% vs. 5%) (1). This was much higher than the rate of 1.8% deep vein thrombosis reported by the pivotal phase III trial (2). Critically ill patients are at very high risk for venous thromboembolism, with some estimates of the incidence as high as 37.2% in patients with sepsis despite prophylaxis (3). When additional information is requested from the manufacturer, the discrepancy between the pivotal trial and package insert is explained as a distinction in the designation of serious adverse event (SAE) and adverse event (AE). In the pivotal phase III trial, only SAEs that occured more frequently than 1% (a subset of all thromboembolic events) were reported whereas in the package insert, all thromboembolic events were merged into a single group that included any thromboembolic event, both serious and non-serious. A majority of patients in this pivotal trial were receiving VTE prophylaxis, but very often, critically ill patients have contraindications to pharmacologic prophylaxis, so not all patients were receiving. In this communication to the manufacturer, there was a trend toward fewer thromboembolic AEs when patients were receiving VTE prophylaxis. Recently, a multicenter observational study of real-world use has reported venous thromboembolism rates similar to those in the pivotal phase III trial (2/133 or 1.5% in this study) (4). Taken together, these data are consistent with the FDA's recommendation to prescribe VTE prophylaxis concurrently (although it is not a contraindication to prescribe if VTE prophylaxis is contraindicated) (1). However, as noted, many patients in the ICU have temporary contraindications to such, which is why standard of care is to address pharmacologic VTE prophylaxis daily on multidisciplinary rounds using a checklist-based system (and if remains contraindicated non-pharmacologic devices are applied to the patient). Given the inherent risks of a patient in septic shock, the benefits of prescribing this medication may outweigh the risks of thrombosis, even in patients not receiving pharmacologic prophylaxis.

The proposed protocol for this study was derived from a number of secondary analyses of the phase III trial, informing us which patients may be most likely to benefit from receiving the drug in septic shock. A secondary analysis of patients with acute kidney injury suggested improved survival through day 28 and increased liberation and therefore avoidance of dialysis through day 7 (5).

References:
1.) Giapreza (angiotensin II) [package insert]. San Diego, CA: La Jolla Pharmaceutical Company. 2018.
2.) Khanna A, English SW, Wang XS, et al. Angiotensin II for the treatment of vasodilatory shock. N Engl J Med. 2017;377:419-430.
3.) Kaplan D, Casper T, Elliot C, et al. VTE Incidence and Risk Factors in Patients With Severe Sepsis and Septic Shock. CHEST 2015 Nov; 148(5): 1224–1230.
4.) Wieruszewski P, Davidson D, Cooper C, et al. Multicenter Study of Angiotensin II Infusion for Refractory Vasodilatory Shock. Crit Care Med. 2020;48(1):724.
5.) Tumlin JA, Murugan R, Deane AM, et al. Outcomes in Patients with Vasodilatory Shock and Renal Replacement Therapy Treated with Intravenous Angiotensin II.Crit Care Med. 2018 Jun;46(6):949-957.

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

1.) To determine if prescription of angiotensin II is associated with faster declines in plasma renin compared to a control group.
2.) To determine if prescription of angiotensin II is associated with improvement of functional renal biomarkers compared to a control group.

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

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

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

This will be a pre-post study built to replicate the introduction of angiotensin II into the clinical practice at UK HealthCare as outlined in the study protocol. 10 patients will be recruited, who receive normal standard of care, and consented to obtain plasma renin levels and biomarkers of renal function (three blood draws). After 10 patients, the next 20 patients meeting eligibility criteria will receive angiotensin II, they will also have blood drawn (four blood draws) to evaluate renin and renal biomarker response to angiotensin II.

Attachments

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

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

Provide the following information:

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

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

Inclusion:
- Medical ICU admission at University of Kentucky Chandler Medical Center
- Septic shock
- Norepinephrine requirement = 0.15 mcg/kg/min for = 30 minutes
- If cirrhosis, norepinephrine requirement = 0.1 mcg/kg/min for = 30 minutes
- KDIGO stage 1 AKI (1.5-1.9 times baseline or = 0.3 mg/dl increase in serum creatinine or urine output < 0.5 ml/kg/hour for 6-12 hours) or worse (this includes stage 2 and stage 3 AKI).

Exclusion:
- Prisoner
- Pregnancy
- Acute occlusive coronary syndrome requiring intervention or acute myocardial infarction of any degree
- Purely cardiogenic shock (no distributive component)
- Mesenteric ischemia
- Acute ischemic stroke

- Hemorrhagic shock
- Active treatment of hepatorenal syndrome targeting a MAP = 65 mm Hg
- Planned withdrawal of care within next 24 hours or no escalation of care
- Patient enrolled in an interventional study
- High likelihood of medical futility in using this drug:
- = 3 vasopressors required to sustain MAP
- Sustained norepinephrine equivalents > 0.5 mcg/kg/min
-COVID-19 positive, or high suspicion of COVID-19 by the attending physician

Attachments

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

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

Please note: Based upon both legal and ethical concerns, the UK IRB does not approve finder's fees or "cold call" procedures made by research staff unknown to the potential participant. The ORI/IRB does not control permission to any UK listserv, mass mailing list, etc. Investigators must secure prior approval for access and use from owners/managers.

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

Potential subjects will be screened based on a screening filter that the study team has previously used in the electronic medical record to screen for studies of septic shock. Once identified, a study team member will approach the patient's nurse and care team to inquire about the study. If allowed, the team member will assess the patient for ability to provide consent as described. If the patient is not eligible to provide informed consent, the legally authorized representative will be approached for written or electronic consent.

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

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

N/A

Attachments

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

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

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

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

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

Once subjects are identified per the above process, an assessment will be made as described in form T by the study team member of whether the patient can provide informed consent. If ineligible, a legally authorized representative will be approached regarding the study. Informed consent will be sought once the patient meets the eligibility criteria as defined in the study protocol. If the legally authorized representative is not physically in the hospital due to visiting restrictions due to COVID-19, an electronic consent process will be sought as follows. The patient's LAR will be contacted via telephone and approached about the study in the same way that the LAR would be if they were physically present. If the LAR is interested in pursuing further, a member of the study team will send the LAR a RedCap link (https://redcap.uky.edu/redcap/surveys/?s=7LWKY4JETE) that has been designed for e-consent in this study. A member of the study team will walk the LAR through the e-consent document, which mirrors the written informed consent document exactly, and answer any questions along the way. If the LAR consents, they will sign the document using the e-sign feature in RedCap. A member of the study team will email the LAR back with a copy of the signed e-consent form.

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

Control group (n=10): Standard of care will be followed for all aspects of care. The only procedure specifically involving research will be blood collection once the patient meets inclusion criteria (time T), 24 hours later (time T + 24 hours), and when the patient no longer requires vasopressor agents to support their blood pressure (defined as off of vasopressors for at least 4 hours). If the patient ceases vasopressor agents within 12 hours of the second blood draw, the third and final blood draw will not be collected.
Intervention group (n=20): Standard of care will be followed for the management of septic shock. At which point the patient meets the inclusion criteria of the study, the patient's treating physician will be approached about the opportunity to offer angiotenisn II to the patient. If the treatment team wishes to pursue, the patient or their LAR will be approached for written informed consent. Angiotensin II will be dosed per the protocol, and the patient will receive blood draw at the time they meet inclusion criteria (time T), 3 hours later (T+3), and 24 hours from angiotensin II initiation (T+24 hours), and when the patient no longer requires vasopressor agents to support their blood pressure (defined as off of vasopressors for at least 4 hours). If the patient ceases vasopressor agents within 12 hours of the third blood draw, the fourth and final blood draw will not be collected. All other aspects of the patient's care will be per the standard of care in the medical intensive care unit. Blood samples will be centrifuged, plasma extracted, and stored at -80 C. Commercial ELISAs will be used for analysis of renin and renal biomarkers (cystatin C, NGAL, renin, angiotensin II, angiotensin 1-7).
COVID specification. Testing positive is a known exclusion criteria for the study. If a patient has results when evaluated for the study, this will be straightforward. However, if the test is pending while the patient is eligible for study entry, this will not make the patient ineligible for the study. If, in the opinion of the attending physician, COVID-19 is highly likely the patient will not be approached for informed consent. Otherwise, if COVID-19 test is pending, the patient or LAR will be approached for informed consent. If the test results as negative, study procedures will be performed as planned. If the test returns positive, the patient will be informed and dropped from the study. We will use their baseline information collected up to that point, but they will no longer receive blood draws or study medication (angiotensin II) once confirmed COVID positive. A case series of angiotensin II has been published in COVID 19

patients, and given the acuity of the disease state in question, it would not be appropriate to wait for a negative COVID test in our judgement.

Attachments

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

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

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

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

Demographics (age, sex, race, past medical history), chief complaint, sequential organ failure assessment score, vasopressor dosing, lactate, requirement for mechanical ventilation, requirement for renal replacement therapy, serum creatinine values, blood pressure. Monitoring of side effects including: venous thromboembolism, arrythmia, extremity hypoperfusion, delirium, new ischemic event, new infection), and any others deemed pertinent per the institution that may be related to angiotensin II. Patient outcomes including: in-hospital mortality, ICU and hospital length of stay, acute kidney injury and needed for renal replacement therapy. Lab values for renin and functional biomarkers of renal function at the time points described (cystatin C, NGAL, angiotensin II, angiotensin 1-7).

Attachments

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

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

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

Co-investigators as outlined in this IRB application. Research personnel to assist with recruitment and sample processing. Laboratory space from Dr. Flannery and Neyra's laboratory.

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

Risks associated with drawing blood from the intravenous line are minimal, but may include discomfort, bruising, soreness, infection, excess bleeding, clotting, light headedness, or fainting. Subjects will have up to 4 teaspoons of blood collected. For those subjects in the intervention arm, risks of receiving angiotensin II include blood clots, thrombocytopenia, tachycardia, fungal infection, delirium, acidosis, hyperglycemia, and peripheral ischemia.

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

Researchers will take steps to keep information confidential. Researchers will not list identifiable information on samples stored in the laboratory, but use a key linked back to a master list maintained on a pass word protected computer. The patients will be in the intensive care unit and subject to the intensive monitoring required from the baseline care of such a population. Once the database has been completed from information collected, identifiable information will be removed and replaced with a subject ID number. The PI will maintain a logbook of the ID number with patient identifiers in a locked cabinet in a locked office.

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

Control group- There is no direct benefit to subjects in the control arm.
Angiotensin II- We do not know if subjects in this group will benefit directly, but hypothesized benefits include less kidney failure (which we are measuring with biomarkers) and fewer vasopressors required to maintain their blood pressure. Risks are outlined in the informed consent document and notably include venous thromboembolism. Given the mortality rate observed with septic shock, the FDA's decision to approve this medication suggest there may be patients that benefit from this drug despite the risks. We have attempted to use the literature to guide our protocol to reflect those patients most likely to benefit. For example, we have focused on acute kidney injury, in which a subgroup analysis from the phase III approval trial suggested improved survival and less dependence on dialysis by day 7 in the subgroup of patients receiving angiotensin II. We have also carefully selected the norepinephrine dose equivalents to reflect those that are severe enough to warrant addition of a second vasopressor, but not high enough that the patient is unlikely to respond to any additional vasopressor (again suggested by a subgroup analysis of the pivotal phase III trial).

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

The only other treatment choice for septic shock at the point that the patient would meet inclusion criteria includes continuing to increase the dose of the vasopressor agent.

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

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

The sources of material collected for this study will primarily come from data documented as part of routine care in the electronic medical record.
Blood specimens will be collected (n=3 in control arm n=4 in angiotensin II arm).

Confidentiality: Specify where the data and/or specimens will be stored and how the researcher will ensure the privacy and confidentiality of both. Please address the following items or indicate if the following has been addressed in a HIPAA or Limited Review form:

- physical security measures (e.g., locked facility, limited access);
- data security (e.g., password-protection, data encryption);
- who will have access to the data/specimens and identifiers;
- safeguards to protect identifiable research information (e.g., coding, links, certificate of confidentiality);
- procedures employed when sharing material or data, (e.g., honest broker if applicable, written agreement with recipient not to re-identify, measures to ensure that subject identifiers are not shared with recipients).
- management after the study

Describe whether data/specimens will be maintained indefinitely or destroyed. If maintained, specify whether identifiers will be removed from the maintained information/material. If identifiers will not be removed, provide justification for retaining them. If the data/specimens will be destroyed, describe how and when the data/specimens will be destroyed. For multi-site studies, the PI consults the study sponsor regarding retention requirements, but must maintain records for a minimum of six years after study closure. Also, specify who will access the identified data/specimens, and why they need access. If applicable, describe what measures will be taken to ensure that subject identifiers are not given to the investigator. If applicable, describe procedures for sharing data/specimens with entities not affiliated with UK.

HIPAA/FERPA Minimal Access Standards: The IRB expects researchers to access the minimal amount of identifiers to conduct the study and comply with applicable HIPAA and Family Educational Rights and Privacy Act (FERPA) requirements. If data are going to be collected, transmitted, and/or stored electronically, for appropriate procedures please refer to the

guidance document "Confidentiality and Data Security Guidelines for Electronic Data" [PDF].

Cloud storage: For storage of data on cloud services other than UK OneDrive, please verify security settings are sufficient and in accordance with respective departmental, UK Corporate Compliance, and/or UK Information Technology requirements.

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

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

Management after study: Describe how the collected data/specimens will be managed after the end of the study. Specify whether identifiers will be removed from the maintained information/material. If identifiers will not be removed, provide justification for retaining them and specify what steps will be taken to secure the data/specimens (e.g., maintaining a coded list of identifiers separate from the data/specimens).

If the data/specimens will be destroyed, describe how, when, and why this will be done. Note that destruction of primary data may violate NIH and NSF retention and sharing requirements, journal publication guidance, and University Data-Retention policies. Additionally, primary data may be necessary for other purposes (to validate reproducibility, for data sharing, or for evidence in various investigations). PIs should carefully consider whether the destruction of data is justified.

The investigator is responsible for retaining signed consent and assent documents and IRB research records for at least six years after study closure, as outlined in the Study Closure SOP [PDF]. If the research falls under the authority of the FDA or other regulatory agencies, or a study sponsor is involved, additional requirements may apply.

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De-identified blood samples will be processed and stored in Dr. Neyra and Flannery's lab with a code linking them back to the master subject list, which will be maintained by the PI in a locked cabinet in a locked office. Data will be input into RedCap using a de-identntfied subject identifier. At the completion of the study, the information obtained from this master logbook will destroyed upon in a manner conducive to HIPAA compliance and accordance with ORI expectations for PHI and destruction of electronic study records per UK Policy A13-050. Records and de-identified electronic data will be kept for at least six years post study closure. At this time, the database will be destroyed according to established procedures.

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

N/A

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

There are no additional costs to subjects.

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

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

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

If relying on an independent agent or committee for DSMB services, it is the PI's responsibility to establish the services with the agent

or committee. Please be reminded that the PI must submit DSMB reports to the IRB via modification or continuing review.

Following enrollment of the 10 patients in the control arm and 10 patients in the angiotensin II arm (i.e. half of the 20 patients that will ultimately receive the drug), we will evaluate the risk of venous thromboembolism and any additional reported thrombotic reports from the 10 patients that have received angiontensin II. Groups will be compared using a Fisher's exact test given the small sample size. Given the concern for safety, if the p-value is 0.15 or less with increased thrombotic events in the angiotensin II group, the open-label study will be stopped. For example, assuming a baseline rate of thrombotic events of 1/10 (10%) in the control arm, if 5/10 patients in the angiotensin II group (50%) experienced a thrombotic event, a Fisher exact test yields p=0.141 and the open-label use of angiotensin II would be stopped due to concern for safety. If thrombotic event differences do not meet this threshold, we will continue with the enrollment of an additional 10 patients to meet the 20 patient enrollment set.

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

Subject complaints will be directed to the primary investigator, who will contact the subjects to discuss their concerns, including potential withdraw from the study or use of their information. If a subject has any concerns or questions about his/her rights as a volunteer in this research, they will be advised to contact staff in the Office of Research Integrity (ORI).

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

○Yes ◉No

Non-English Speaking Subjects or Subjects from a Foreign Culture

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

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

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

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

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

○Yes ◉No

HIV/AIDS Research

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

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

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

PI-Sponsored FDA-Regulated Research

Is this an investigator-initiated study that:

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

○Yes ◉No

PI-Sponsored FDA-Regulated Research

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

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

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

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

○Yes ○No

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

Attachments

HIPAA

Is HIPAA applicable? ◉ Yes ○ No

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

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

☐ HIPAA De-identification Certification Form

☑ HIPAA Waiver of Authorization

Attachments

Attach Type	File Name
Waiver	Form K.pdf

STUDY DRUG INFORMATION

The term drug may include:

- FDA approved drugs,
- unapproved use of approved drugs,
- investigational drugs or biologics,
- other compounds or products intended to affect structure or function of the body, and/or
- complementary and alternative medicine products such as dietary supplements, substances generally recognized as safe (GRAS) when used to diagnose, cure mitigate, treat or prevent disease, or clinical studies of e-cigarettes examining a potential therapeutic purpose.

Does this protocol involve a drug including an FDA approved drug; unapproved use of an FDA approved drug; and/or an investigational drug?

◉ Yes ○ No

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

LIST EACH DRUG INVOLVED IN STUDY IN THE SPACE BELOW

Drug Name:

Angiotensin II

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

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

☑ Investigational Drug Service (IDS) UK Hospital

Other Location:

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

○ Yes ◉ No

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

IND Submitted/Held by:

Sponsor: ☐ Held By:

Investigator: ☐ Held By:

Other: ☐ Held By:

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

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

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

Attachments

Attach Type	File Name
StudyDrug	Label.pdf
StudyDrug	Study Drug IRB.pdf

STUDY DEVICE INFORMATION

A DEVICE may be a:

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

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

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

○ Yes ◉ No

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

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

LIST EACH DEVICE BEING TESTED IN STUDY IN THE SPACE BELOW

Device Name:

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

○ Yes ○ No

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

IDE/HDE Submitted/Held by:

Sponsor: ☐ Held By:

Investigator: ☐ Held By:

Other: ☐ Held By:

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

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

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

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

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

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

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

Attachments

RESEARCH SITES

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

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

UK Sites

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

Schools/Education Institutions

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

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

Other Medical Facilities

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

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

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

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

Attachments

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

If **YES**, you must describe the plan for the management of reporting unanticipated problems, noncompliance, and submission of

protocol modifications and interim results from the non-UK sites in the E-IRB "Research Description" section under *Resources*.

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

RESEARCH ATTRIBUTES

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

☐ Not applicable

Check All That Apply

☐ Academic Degree/Required Research
☐ Aging Research
☐ Alcohol Abuse Research
☐ Cancer Research
☐ Certificate of Confidentiality
☑ CCTS-Center for Clinical & Translational Science
☑ Clinical Research
☑ Clinical Trial
☐ Clinical Trial Multicenter(excluding NIH Cooperative Groups)
☐ Clinical Trial NIH cooperative groups (i.e., SWOG, RTOG)
☐ Clinical Trial Placebo Controlled Trial
☑ Clinical Trial UK Only
☑ Collection of Biological Specimens
☐ Collection of Biological Specimens for Banking
☐ Community-Based Participatory Research
☐ Data & Safety Monitoring Board
☐ Data & Safety Monitoring Plan
☐ Deception
☐ Drug/Substance Abuse Research
☐ Educational/Student Records (e.g., GPA, test scores)
☐ Emergency Use (Single Patient)
☐ Genetic Research
☐ Gene Transfer
☐ GWAS (Genome-Wide Association Study) or NIH-funded study generating large scale genomic data
☐ International Research
☐ Internet Research
☐ Planned Emergency Research Involving Waiver of Informed Consent
☐ Pluripotent Stem Cell Research
☐ Recombinant DNA
☐ Survey Research
☐ Transplants
☐ Use of radioactive material, ionizing radiation, or x-rays [Radiation Safety Committee review required]
☐ Vaccine Trials

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

- Cancer Research (MCC PRMC)
- Certificate of Confidentiality (look up "Confidentiality/Privacy...")
- CCTS (Center for Clinical and Translational Science)
- Clinical Research (look up "What is the definition of....)
- Clinical Trial (look up "What is the definition of.....)

  Determine if research meets NIH definition of clinical trial;
  *Reminder: Ensure compliance with applicable requirements including:
  - Clinicaltrials.gov registration;
  - Good Clinical Practice (GCP) training; and
  - Consent Posting Requirement for federal funded trials.

- Collection of Biological Specimens for Banking (look up "Specimen/Tissue Collection. ")
- Collection of Biological Specimens (look up "Specimen/Tissue Collection. ")
- Community-Based Participatory Research (look up "Community-Engaged. ")
- Data & Safety Monitoring Board (DSMB)

  *For Medical IRB: Service Request Form for CCTS DSMB

- Data & Safety Monitoring Plan
- Deception*

  *For deception research, also go to the E-IRB Application Informed Consent section, checkmark and complete "Request for Waiver of Informed Consent Process"

- Emergency Use (Single Patient) [attach Emergency Use Checklist] (PDF)
- Genetic Research (look up "Specimen/Tissue Collection. ")
- Gene Transfer
- HIV/AIDS Research (look up "Reportable Diseases/Conditions")
- Screening for Reportable Diseases [E2.0000] (PDF)
- International Research (look up "International & Non-English Speaking")
- NIH Genomic Data Sharing (GDS) Policy (PDF)
- Planned Emergency Research Involving Waiver of Informed Consent*

  *For Planned Emergency Research Involving Waiver of Informed Consent, also go to the E-IRB Application Informed Consent section, checkmark and complete "Request for Waiver of Informed Consent Process"

- Use of radioactive material, ionizing radiation or x-rays for research

FUNDING/SUPPORT

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

☐ Not applicable

Check All That Apply

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

Other:

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

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

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

La Jolla Pharmaceutical Company (providing angiotensin II and funds for renin assay)

Add Related Grants

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

Add Related Grants

Grant/Contract Attachments

Attach Type	File Name
GrantContract	UK_Collaborative Study_Approval Letter.pdf

The research involves use of Department of Defense (DoD) funding, military personnel, DoD facilities, or other DoD resources. (See DoD SOP [PDF] and DoD Summary [PDF] for details)

○Yes ◉No

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

DOD SOP Attachments

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

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

OTHER REVIEW COMMITTEES

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

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

◉ Yes ○ No

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

Attachments

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

ADDITIONAL INFORMATION/MATERIALS

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

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

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

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

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

Protocol/Product Attachments

Attach Type	File Name
AddInfoProtocol	Final Proposal.docx

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

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

Additional Materials:

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

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

Attachments

Attach Type	File Name
AdditionInfoConsiderations	57411 Flannery.pdf

Statistical Analysis

Continuous data will be described using medians and interquartile ranges. Discrete data will be described as counts and percentages. Changes in biomarker measurements will be calculated by subtracting the biomarker measurement at subsequent timepoint from the baseline biomarker measurement at enrollment. Assuming non-normal distributions of biomarker measurements with extreme elevations as well as skewness of the data for lengths of stay, continuous variables will be compared using the Mann-Whitney U test while discrete data will be compared between groups using chi-squared or Fisher's exact test as appropriate. A p-value <0.05 will be considered statistically significant.

Interim Analysis

Following enrollment of the 10 patients in the control arm and 10 patients in the angiotensin II arm (i.e. half of the 20 patients that will ultimately receive the drug), we will evaluate the risk of venous thromboembolism and any additional reported thrombotic reports from the 10 patients that have received angiotensin II. Groups will be compared using a Fisher's exact test given the small sample size. Given the concern for safety, if the p-value is 0.15 or less with increased thrombotic events in the angiotensin II group, the open-label study will be stopped. For example, assuming a baseline rate of thrombotic events of 1/10 (10%) in the control arm, if 5/10 patients in the angiotensin II group (50%) experienced a thrombotic event, a Fisher exact test yields $p=0.141$ and the open-label use of angiotensin II would be stopped due to concern for safety. If thrombotic event differences do not meet this threshold, we will continue with the enrollment of an additional 10 patients to meet the 20 patient enrollment set.