

## 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 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 download the IRB Introduction Packet for more details [\[PDF\]](#). 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 IRBs review 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 or studies that involves 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 [\[see categories\]](#);
- by expedited review [\[see categories\]](#);

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 see the IRB Introduction Packet [\[PDF\]](#).

## EXPEDITED CERTIFICATION

### To Be Completed Only If Protocol is to Receive Expedited Review

#### Applicability

- A. Research activities that (1) present no more than [\\*minimal risk](#) to human subjects, and (2) involve only procedures listed in one or more of the following categories, may be reviewed by the IRB through the expedited review procedure authorized by [45 CFR 46.110](#) and [21 CFR 56.110](#). The activities listed should not be deemed to be of minimal risk simply because they are included on this list. Inclusion on this list merely means that the activity is eligible for review through the expedited review procedure when the specific circumstances of the proposed research involve no more than minimal risk to human subjects.
- B. The categories in this list apply regardless of the age of subjects, except as noted.
- C. The expedited review procedure may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.
- D. The expedited review procedure may not be used for classified research involving human subjects.
- E. IRBs are reminded that the standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review—expedited or convened—utilized by the IRB.

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

Check the appropriate categories that apply to your research project:

Study was originally approved by the full IRB at a convened meeting.

1) Clinical studies of drugs and medical devices only when condition (a) or (b) is met.

- A. Research on drugs for which an investigational new drug application ([21 CFR Part 312](#)) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)
- B. Research on medical devices for which (i) an investigational device exemption application ([21 CFR Part 812](#)) is not required\*; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.\*\*

\*A determination on whether an IDE application is required may be made by the FDA or based on a Non-Significant Risk (NSR) determination by the convened IRB. Unless the study has documentation from FDA indicating that an IDE application is not required, it may not be approved under expedited mechanisms.

\*\* An approved Device used in research according to its approved labeling is considered Exempt from IDE requirements- [21 CFR 812.2\(c\)](#)

2) Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

- A. From healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or
- B. From other adults and children\* considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

NOTE: Intravenous (IV), Port, Central, or any other lines are NOT eligible under this category even if the research involves "minimal risk".

\*In Kentucky, "child/children" refers to all individuals less than 18 years of age unless the individual(s) is/are legally emancipated. (See Informed Consent SOP [\[PDF\]](#) for discussion of "Emancipated Individuals" under Kentucky state law.) Individuals less than 18 years of age who are not emancipated meet the federal definition for "child" (e.g., DHHS, FDA, and U.S. Department of Education). Children are defined in the HHS regulations as "persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted." [45 CFR 46.402\(a\)](#) If conducting research outside the state of Kentucky, you are responsible for complying with applicable state law.

3) Prospective collection of biological specimens for research purposes by noninvasive means. Examples:

- A. Hair and nail clippings in a nondisfiguring manner;
- B. Deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction;
- C. Permanent teeth if routine patient care indicates a need for extraction;
- D. Excreta and external secretions (including sweat);
- E. Uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue;
- F. placenta removed at delivery;
- G. Amniotic fluid obtained at the time of rupture of the membrane prior to or during labor;
- H. Supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques;
- I. Mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings;
- J. Sputum collected after saline mist nebulization.

□ 4) Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.) Examples:

- A. Physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy;
- B. Weighing or testing sensory acuity;
- C. Magnetic resonance imaging;
- D. electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography;
- E. moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

□ 5) Research involving materials (data, documents, records, or specimens) that have been collected or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis). (Note: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. [45 CFR 46.101\(b\)\(4\)](#). This listing refers only to research that is not exempt.)

□ 6) Collection of data from voice, video, digital, or image recordings made for research purposes.

□ 7) Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. (Note: Some research in this category may be exempt from the HHS regulations for the protection of human subjects [45 CFR 46.101\(b\)\(2\) and \(b\)\(3\)](#). This listing refers only to research that is not exempt.)

**PROJECT INFORMATION**

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

IRB Share / Novel Actions of Metformin to Augment  
Resistance Training Adaptation in Older Adults

**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.



MASTERS

Anticipated Ending Date of Research Project: 12/31/2019

Number of human subjects  40

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

## PI CONTACT INFORMATION

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

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

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

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

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

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

### Note: Principal Investigator (PI) role for E-IRB access

The PI is the individual holding primary responsibility on the research project with the following permissions on the E-IRB application:

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

### [Change Principal Investigator:](#)

First Name:	<input type="text" value="Charlotte"/>	Room# & Bldg:	<input type="text" value="900 S Limestone"/>
Last Name:	<input type="text" value="Peterson"/>	Speed Sort#:	<input type="text" value="40536"/>
Department:	<input type="text" value="Health Sciences - Rehabilitati ..."/>	Degree:	<input type="text" value="PhD"/>
PI's Employee/Student ID#:	<input type="text" value="10160796"/>	Rank:	<input type="text"/>
PI's Telephone #:	<input type="text" value="218-0476"/>	Dept Code:	<input type="text" value="7N600"/>
PI's e-mail address:	<input type="text" value="Charlotte.Peterson@uky.edu"/>	PI's FAX Number:	<input type="text"/>
PI is R.N. <input type="radio"/> Yes <input checked="" type="radio"/> No		Trained:	<input type="text" value="Yes"/>
		Date Trained:	<input type="text" value="12/15/2017"/>

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

Yes  No

**RISK LEVEL**

Indicate which of the categories listed below accurately describes this protocol

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

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

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

**SUBJECT DEMOGRAPHICS**

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

Indicate the targeted/planned enrollment of the following members of minority groups and their subpopulations

**(Please note: The IRB will expect this information to be reported at Continuation Review time):**

Enter Numbers Only!		
Ethnic Origin	#Male	#Female
American Indian/Alaskan Native:	<input type="text" value="0"/>	<input type="text" value="0"/>
Asian:	<input type="text" value="1"/>	<input type="text" value="1"/>
Black African American:	<input type="text" value="2"/>	<input type="text" value="3"/>
Hispanic/Latino:	<input type="text" value="0"/>	<input type="text" value="0"/>
Native Hawaiian/Pacific Islander:	<input type="text" value="0"/>	<input type="text" value="0"/>
White/Caucasian:	<input type="text" value="16"/>	<input type="text" value="17"/>
Other or Unknown:	<input type="text"/>	<input type="text"/>

If unknown, please explain why:

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

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

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

**ADDITIONAL INFORMATION:**

Please visit the [IRB Survival Handbook](#) under the named topic:

- Children/Emancipated Minors
- Students as Subjects
- Prisoners
- Impaired Consent Capacity Adults: Link to required [Form](#)

And/Or:

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

## Material

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

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

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

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

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

Yes  No

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

**Examples of such conditions include:**

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

Attachments

## INFORMED CONSENT/ASSENT PROCESS/WAIVER

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

Additional Resources:

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

### Consent/Assent Tips:

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

Document Types that do NOT get an IRB approval stamp are:

- "Highlighted Changes",
- "Phone Script", and
- "Sponsor's Sample Consent Form".

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).

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 (and/or Assent 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

#### Attachments

Attach Type	File Name
Informed Consent/HIPAA Combined Form	Metformin IRB Approval 042516.pdf
Informed Consent/HIPAA Combined Form	Form C with HIPAA- Metformin 040816 clean.pdf
Informed Consent/HIPAA Combined Form	Initial Phone Screening Guide and Questionnaire Metformin- 060214 clean.pdf

Request for Waiver of Informed Consent Process

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

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

#### SECTION 1.

Check the appropriate item:

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

I am requesting alteration of the informed consent process.

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

**SECTION 2.**

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

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

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

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

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

Request for Waiver of Documentation of Informed Consent Process

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

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 must be asked whether (s)he wants to sign a consent form; if the participant agrees to sign a consent form, 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):

## STUDY PERSONNEL

Do you have study personnel who will be assisting with the research?

After selecting "Yes" or "No" you must save by hitting the 'Save Study Personnel Information' button. 

Yes  No

## Manage Study Personnel

Identify other study personnel assisting in research project:

- The individual listed as PI in the 'PI Contact Information' section should NOT be added to this section.
- If the research is being completed to meet the requirements of a University of Kentucky academic program, the faculty advisor is also considered study personnel and should be listed as such below.
- Role: DP = Editor (individual can view, navigate, and edit the application for any review phase (IR, CR, MR) or 'Other Review', and submit Other Reviews on behalf of the PI.)
- Role: SP = Reader (individual can view and navigate through the currently approved application only.)

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

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

Study personnel assisting in research project: 

## Add Personnel

My Study Personnel	Last Name	First Name	Responsibility In Project	Role	A C	Contact	Degree	StatusFlag	(HSP)	(HSP)Date	Removed?	Last Updated	Recorded Training	SFI
<a href="#">Details</a>	Bayes	Ashley	Project Assistance/Support	SP	N	N		S	Y	09/04/2017	N	09/24/2018	<a href="#">10937267</a>	N
<a href="#">Details</a>	Bush	Heather	Data Analysis/Processing	SP	N	N		P	Y	07/22/2016	N	09/24/2018	<a href="#">10164646</a>	N
<a href="#">Details</a>	Chamblin	Lisa	Project Assistance/Support	SP	N	N		P	Y	08/10/2016	N	09/24/2018	<a href="#">00007063</a>	N
<a href="#">Details</a>	Dungan	Cory	Project Assistance/Support	SP	N	N		P	Y	08/04/2016	N	09/24/2018	<a href="#">12220934</a>	N
<a href="#">Details</a>	Holbrook	Kathryn	Project Assistance/Support	SP	N	N		P	Y	01/06/2016	N	09/24/2018	<a href="#">00006107</a>	N
<a href="#">Details</a>	Hommel	Leta	Project Assistance/Support	SP	N	N		P	Y	02/24/2017	N	09/24/2018	<a href="#">00006844</a>	N
<a href="#">Details</a>	Kern	Philip	Medical Supervisor	SP	Y	N		P	Y	08/01/2017	N	09/24/2018	<a href="#">10684761</a>	N
<a href="#">Details</a>	Long	Douglas	Co-Investigator	DP	N	Y			Y	08/01/2016	N	09/24/2018	<a href="#">10037901</a>	N
<a href="#">Details</a>	Moylan	Jennifer	Project Assistance/Support	SP	N	N		P	Y	09/06/2017	N	09/24/2018	<a href="#">00047876</a>	N
<a href="#">Details</a>	Peck	Bailey	Project Assistance/Support	SP	N	N		P	Y	12/30/2017	N	09/24/2018	<a href="#">12158518</a>	N
<a href="#">Details</a>	Rice	Linda	Project Assistance/Support	SP	N	N		P	Y	09/07/2017	N	09/24/2018	<a href="#">00006902</a>	N
<a href="#">Details</a>	Ross	Dorothy	Project Assistance/Support	SP	N	N		P	Y	12/01/2017	N	09/24/2018	<a href="#">10172013</a>	N
<a href="#">Details</a>	Villasante Tezanos	Alejandro	Data Analysis/Processing	SP	N	N		P	Y	05/17/2018	N	09/24/2018	<a href="#">10875806</a>	N
<a href="#">Details</a>	Walton	Rosicka	Project Assistance/Support	SP	N	N		P	Y	11/28/2017	N	09/24/2018	<a href="#">10877083</a>	N

## RESEARCH DESCRIPTION

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

### Workaround(s):

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

**Background:** Provide an introduction and background information. Describe past experimental and/or clinical findings leading to the formulation of your study. For research involving investigational drugs, describe the previously conducted animal and human studies. You may reference grant application/sponsor's relevant protocol pages and attach as an appendix in the E-IRB "Additional Information" section. 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.

Muscle mass and strength are critical determinants not only of a person's quality of life and functional independence, but also metabolic health, as muscle is the organ primarily responsible for insulin-mediated glucose uptake. The elderly suffer obligatory losses of muscle mass and strength, exacerbated by illness and physical inactivity. Progressive resistance exercise training (PRT) is the most effective intervention identified to improve muscular strength, and combat the muscle atrophy of aging (sarcopenia); however, overall the muscle response to PRT is blunted in the elderly and variability of response increased, with some individuals actually losing muscle mass. The Bamman and Peterson labs have independently been studying the molecular and cellular mechanisms underlying the "non-responder" phenotype, with the goal of identifying novel intervention strategies to promote mass and strength gains to improve function. We hypothesize that the abundance of anti-inflammatory, alternatively activated M2 macrophages in muscle predicts response to PRT in the elderly; those with the highest number of M2 macrophages and lowest inflammatory gene expression prior to the start of training gained the most mass. Further, we determined that metformin treatment increased M2 macrophage abundance, and decreased inflammatory cytokine gene expression. These provocative findings have led us to our central hypothesis that adjuvant metformin may improve the responses to PRT in the elderly by altering the muscle tissue inflammatory environment, thereby enhancing mechanisms that drive PRT-induced myofiber hypertrophy. We are well-positioned to test this hypothesis and to determine the translational potential of PRT + metformin to synergistically combat sarcopenia and extend human health span. We propose a blinded, placebo-controlled PRT study to determine metformin's physiologic and cellular effects in reducing deleterious consequences of aging on muscle.

**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.

Aim 1. Determine if metformin treatment augments skeletal muscle size and strength gains in conjunction with PRT in older adults. Participants over age 65 years old will be recruited and randomized to receive either placebo or metformin for 2 weeks followed by a 14 week PRT program with continued drug/placebo treatment. Gains in muscle size and strength, and changes in insulin sensitivity, will be quantified. Muscle biopsies from the vastus lateralis will be obtained at the time of recruitment, following pre-exercise metformin/placebo treatment, and at the end of training for quantification of myofiber cross-sectional area. In this way, the ability of metformin to improve muscle response to PRT in the elderly will be determined. Aim 2. Identify cellular and molecular responses in muscle to metformin which are associated with improved response to PRT. Macrophages, inflammatory gene expression and anabolic and pro-inflammatory signaling pathways following metformin and after PRT with continued metformin or placebo, will be examined in muscle. We hypothesize that metformin will increase the relative abundance of M2 macrophages and reduce the overall inflammatory state of muscle, that will promote satellite cell-mediated hypertrophy, effectively converting non-responders to responders. In addition, we hypothesize that subjects receiving metformin will have a greater anabolic response due to changes in both mTORC1 signaling/inhibition and mitochondrial content, activity, and mitophagy. mRNA and protein expression will be assessed for mTORC1 signaling, mTORC1 inhibition, and markers of mitophagy to quantify the effects of metformin on mTORC1 activity and markers of mitophagy. Immunohistochemistry (IHC) will be used to correlate muscle fiber cross-sectional area (CSA) gains with changes in mitochondrial content, activity and mitophagy. Mitochondrial bioenergetics will be assessed using the Oroboros Oxygraph. Aim 3. Explore mechanisms underlying metformin effects on muscle response to training using a human muscle cell culture system that models exercise and the muscle microenvironment. Isolated myoblasts, differentiated into myotubes from the biopsy muscle, will be stretched on a Flexcell tension system that induces myotube hypertrophy in vitro. Co-culture of myotubes with monocytes or inflammatory M1 macrophages, in the presence or absence of metformin, will determine the impact of metformin on inflammatory gene expression in both cell types and changes in response to stretch, which will be correlated to in vivo response to PRT. The long term goal of this study is to enable the development of targeted interventions to effectively combat sarcopenia, thereby maintaining functional independence and improving metabolic regulation and quality of life in the elderly. Prospective identification of individuals likely to be refractory to routine exercise programs, and determining the effectiveness of metformin in improving the muscle growth response to PRT, may contribute to the development of a low cost, personalized approach to maintain or restore skeletal muscle mass and strength in the elderly.

**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. (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 describe the repository design and operating procedures. For relevant information to include, see question 22 of the UK IRB "Frequently Asked Questions (FAQs) on the Return of Research Results or Incidental Research Findings" [[PDF](#)].

We have assembled a dual-site team (UK and UAB) of established investigators with complementary skills and a wealth of pertinent experience to conduct a randomized, double-blind, placebo-controlled trial that is centered on a novel, alternative use of metformin. This will be the first known metformin repurposing trial to test the potential impact of combined exercise-drug therapy on muscle mass and function, and it will be conducted in an aging cohort most in need of a treatment that maximizes muscle regrowth and strength gain. The two site design ensures that recruitment goals will be met and data analyzed within the duration of the granting period. Because a more diverse population will be studied than at either site alone, results obtained will be more generalizable. Subjects will also be stratified and randomized by site and by functional status. Data Collection Schedule (Table 1). This protocol involves ~17 wk of participation. Subjects will complete assessments at the CTSA-sponsored clinical services cores at each site. Pre-treatment. Following physical exam and detailed screening, baseline tests will include: (i) short physical performance battery (SPPB), functional tests of balance, gait speed, ; (ii) a fasting blood draw to assess liver and kidney function, glucose, insulin, and electrolytes (repeated at midpoint of the PRT period to monitor liver and kidney function for safety) Vit D and other blood tests that may be related to muscle function or insulin resistance could also be assessed ; cell isolation; (iii) an oral glucose tolerance test (OGTT); (iv) whole body dual-energy x-ray absorptiometry (DXA) scan along with circumferences; (v) vastus lateralis muscle biopsy and mid-thigh CT; (vi) 4 day diet record and physical activity monitoring; and (vii) self reported quality of life involving several questionnaires. Subjects will also be introduced to the strength and power testing. Subjects will then be randomized and sent home with instructions and a 2 wk supply of metformin or placebo (in double-blind fashion). Week 2. After 2 wk of metformin/placebo, fasting blood, and muscle biopsy will be repeated. Baseline strength and power tests will be performed and pills counted for compliance. Strength and power testing at this time will be primarily used as a second familiarization and practice testing session, to account for the well-known motor learning effects that can dramatically influence performance during maximal testing of naïve subjects. Resistance training will then be introduced and progressed over a 2 wk period. Week 4. After the first 2 wk of resistance training familiarization and ramping, strength and power testing will be repeated and considered true baseline muscle performance, followed by 12 wk of PRT at full volume and intensity. Week 9. Strength and power testing will be performed halfway through the PRT program along with a safety check blood draw. Week 16. All dependent variables will be re-assessed within 5 days post-training; strength, power and SPPB on the final day of training; muscle biopsy, OGTT, blood draw, CT, circumferences, questionnaires, and DXA on subsequent visits. Long Term Follow Up. We plan to contact those individuals that may be interested in returning to perform certain assessments including strength and power, quality of life, as well as physical function and activity monitoring at 26 and 52 weeks after initial evaluation. During the 14 wk of PRT (2 wk of familiarization and ramping; 12 wk of full volume PRT), participants will report 3 times per wk to exercise and to obtain the necessary number of capsules. The exercise physiologists supervising training and compliance and technicians/nurses performing scans/tests will be blinded to drug treatment and will perform all analyses using methods standardized between sites. Retention. We expect voluntary attrition rate to be approximately 20%, slightly higher than in our prior resistance training studies in deconditioned older adults (15%). Compliance. Ideally all subjects would attend 100% of scheduled resistance exercise sessions and will consume all prescribed doses of metformin or placebo, but we have sufficient experience with these types of intensive trials to recognize that this ideal scenario is not realistic. For this project, the goal will be 3 d/wk resistance training, but subjects who complete at least 5 of 6 sessions every two weeks will be considered in good standing. Subjects will be given pre-configured dosages with instructions to return unused containers; visiting the facility 3 times per week for exercise training will facilitate compliance. In cases where a pattern of noncompliance develops, the study coordinators will prompt participants with evening phone calls.

#### Attachments

Attach Type	File Name
StudyDesign	Form B- Metformin 031417 Clean.doc

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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 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 these groups 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.

One hundred males and females (n=60 at UAB completed in years 1-4; n=40 at UK in the first 2½ years of the award) =65 years of age with a short physical performance battery (SPPB) score of >3 (score range 0-12) will be studied. These represent non-disabled and mobile individuals who are able to participate in the functional testing and resistance exercise. The recruitment distribution between sites is based on past recruitment/retention experience with PRT trials, and it will enable UK team members to focus on tissue analyses in years 3-5. Given the anticipated attrition rate of 20%, we will recruit 120 participants (72 UAB and 48 UK) to achieve a final sample size of 100 (50 metformin, 50 placebo), which will allow sufficient power for "as observed" comparisons. Approximately equal numbers of men and women of all races and ethnicities will be recruited from the Centers on Aging, through the CTSA Volunteer Opportunities Websites at both institutions, and through general advertisements. Human subjects recruited into this study will have no history of resistance training (>2x per week consistently) within the past year, and no contraindications to being in the study (see inclusion/exclusion criteria below). Inclusion criteria • =65 years of age. • Independently mobile with a SPPB score 3-12. • Access to transportation. • Capable of providing informed consent (cognitively intact). Exclusion criteria • Obesity (BMI>30) • Serum creatinine >1.4 because of risk of lactic acidosis with metformin. • History of regular resistance training within the past year. • History (or ECG evidence) of previous myocardial infarction, history of congestive heart failure. • Current angina pectoris or symptoms of myocardial ischemia or congestive heart failure. • Chronic aspirin or NSAID use (unless it can be safely stopped prior to the biopsies), and any other use of an anticoagulant (e.g., Coumadin) or history of bleeding. • History of alcoholism or liver disease. • History of hypo- or hyper-coagulation disorders including subjects taking Coumadin. • Any end-stage disease and/or a life expectancy less than one year. • Neurological, musculoskeletal, or other disorder that would preclude them from completing resistance training and all performance tests. • Uncontrolled hypertension. • Diabetes mellitus as demonstrated with- HgbA1C>6.5, or fasting glu>126 mg/dl. • Any other medical condition that would interfere with testing or increase one's risk of complications during exercise, as judged by the study physicians. • Any other condition or events considered exclusionary by the PI and/or physician, such as non-compliance. • Lidocaine allergy (1% lidocaine is the local anesthetic used during the muscle biopsy procedure). Estrogen/progesterone hormone (HRT) replacement therapy will not be an inclusion or exclusion criterion as this does not affect gains in muscle strength or lean mass during resistance training.

#### Attachments

**Subject Recruitment Methods & Privacy:** 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. If applicable, describe proposed outreach programs for recruiting women and minorities as participants in clinical research.

Please note: Based upon both legal and ethical concerns, the UK Medical Institutional Review Board (IRB) will not approve finder's fees for research studies.

Men and women =65 years of age, representative of the racial and ethnic makeup of greater Birmingham, Alabama and greater Lexington, Kentucky, will be recruited from Centers on Aging at both institutions and through general advertisements. In addition, both institutions have extensive marketing and recruitment programs, involving several volunteer databases including ResearchMatch where eligible subjects can be contacted, posterboards and flyers located throughout the facilities, a community engagement program that has close ties to community organizations, and recruitment specialists who can advise us on optimal strategies.

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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" 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. [i](#)

Men and women =65 years of age, representative of the racial and ethnic makeup of greater Birmingham, Alabama and greater Lexington, Kentucky, will be recruited from Centers on Aging at both institutions and through general advertisements. In addition, both institutions have extensive marketing and recruitment programs, involving several volunteer databases including ResearchMatch where eligible subjects can be contacted, posterboards and flyers located throughout the facilities, a community engagement program that has close ties to community organizations, and recruitment specialists who can advise us on optimal strategies.

#### Attachments

Attach Type	File Name
Advertising	REHAB-108_flyer_PR.pdf
Advertising	REHAB-108_flyer_RM(PR).pdf
Advertising	REHAB-108_spotlight22x28 (PR).pdf
Advertising	REHAB-108_newspaper3x5APPROVED.pdf
Advertising	REHAB-108_flyer2(pr).pdf



**Informed Consent Process:** 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 (Note: all individuals authorized to obtain informed consent should be designated as such in the E-IRB "Study Personnel" section of this application), 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. 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 (i.e., research involving adult subjects with impaired consent capacity) 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. For additional information, see the [Informed Consent Standard Operating Procedures \(SOPs\)](#) (PDF).

#### *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 "[University of Kentucky Issues to be Addressed and Sample Consent Language for Tissue/Specimen Repositories or Individual Studies Banking Material for Future Use](#)" (PDF).

All participation will be on a voluntary basis and each participant will be required to sign an approved IRB consent form prior to participation in the study protocol. All procedures included in the study will be explained in detail (including approximate time commitment and potential risks) to the subjects by a member of the research team designated to do so. After the participant has been completely informed, all questions that may arise will also be answered so that the subject is fully aware of the study design and what they will be asked to do. The subject will be reminded that they may withdraw from the study at any time, that all information will remain confidential, and of the steps that will be taken in case of an adverse event. The original signed consent form will be filed and available for review at any time during the study duration and to ensure confidentiality of the collected data. All subjects will receive a copy of the signed consent form for their personal records.

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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.

Respondents that appear to qualify based on an initial screen (phone or web; see submitted forms), will come in for a face-to-face interview that will begin with the informed consent process. Each volunteer must pass a careful history which will include additional questionnaires such as the PAR-Q and other health screens, a physical exam, electrocardiogram (ECG). These will be performed in the CCTS under supervision of the study physician, PA, CCTS nursing personnel, and an exercise physiologist. Respondents will also perform the Short Physical Performance Battery (SPPB) and complete a fasting blood draw where some of the blood can also be prepared for monocyte isolations. Final enrollment decisions will be contingent upon successful completion of all screens, including passing the physical exam and acceptable laboratory results (creatinine, glucose, liver enzymes, TSH, CBC with platelets, HgbA1C). Short Form 36 (SF-36). The SF-36 survey is a multi-item scale designed to assess health related quality of life among eight domains. These include physical functioning, role limitations due to physical health problems, bodily pain, general health perceptions, vitality (energy and fatigue), social functioning, role limitations due to emotional problems, and mental health. It has demonstrated excellent reliability and validity in older adults and across various populations. Physical Activity Measures. The Physical Activity Survey for the Elderly (PASE) as well as physical activity monitors will be used in this study. The PASE is a self report or interview based measure designed to capture and assess occupational, household, and leisure activities typically performed by older adults including those of lighter intensity. Time spent participating in each activity area is multiplied by a weighted value that reflects the amount of energy expended by an older person engaged in that activity. These weighted values are then summed to yield a composite PASE score. This questionnaire has been found to be both reliable and valid among community dwelling and physically disabled older adults. Our physical activity monitor will be worn on the wrist and will have accelerometry, HR monitoring, and sleep pattern capabilities. PROMIS modules. PROMIS uses modern measurement theory to assess patient-reported health status for physical, mental, and social well-being to reliably and validly measure patient-reported outcomes (PROs) for clinical research and practice. PROMIS instruments are generated from item banks. PROMIS' measures can be used as primary or secondary endpoints in clinical studies of the effectiveness of treatment. SPPB functional testing. The three timed standing balance tests (side-by-side, semi-tandem and tandem), 4-meter gait speed test performed twice, and timed repeated chair sit to stand (5 times) will be performed 1. Performance for each set of tasks is scored (0-4), with a summary score of 0-12. Muscle strength and power testing. Voluntary,

dynamic strength will be evaluated by testing a one repetition max (1-RM), defined as the maximal load that a subject can lift one time with proper form through a full range of motion, via our well-established methods 2-4 that have been standardized across sites. After warm-up, single repetition trials (separated by 1-2 min rest) are performed with increasing resistance until two failed attempts at a given load. The last successfully lifted load with good form will be recorded as the 1-RM. We will also evaluate maximum voluntary isometric knee extension strength using our established methods on a Biodex 4 dynamometer 5, available at both sites. Knee extension concentric power will also be determined using the Biodex set on isotonic mode to allow for variable velocities with a constant external load equal to 40% of maximum voluntary isometric strength. OGTT. A standard 2 hr OGTT will be performed after a 8-12 hr fast using 75 g glucose. Blood will be drawn before and 30, 60, 90 and 120 min after ingestion for measurement of glucose and insulin, and the Matsuda index, which correlates well with the euglycemic clamp 6 will be used to calculate insulin sensitivity. DXA. Body composition (whole body, regional fat and lean mass) and bone mineral density will be determined using a Lunar Prodigy (UAB) and an IDXA (UK) and standardized methods for regional partitioning. Data quality will be assured by phantom calibrations. Each participant will receive a DXA scan performed at the CCTS in the University of Kentucky Medical Center by study personnel trained in this procedure. The subjects will be instructed to remove all objects such as jewelry or eyeglasses and will wear a hospital gown, or a light weight shirt and shorts (containing no metal) during the scanning procedure. If a woman of childbearing potential is to be scanned, a pregnancy test will be conducted prior to the scan. The scan takes approximately 8-10 minutes to complete. All scans will be analyzed by a trained and certified investigator using the GE Lunar software version 10.0. DXA bone mineral content (BMC; kg), DXA bone mineral density (BMD; g/cm<sup>2</sup>), DXA fat-free mass (FFM; kg), DXA mineral-free lean mass (MFL; kg), DXA fat mass (Fat; kg), and DXA percent fat (%Fat) will be assessed. Anthropometry (Circumferences). Circumferences will be taken at various places on the upper body including the waist, abdomen, and hip etc. All measures will be taken by rotating through measurement sites and taking duplicate measures at each site if measures are not within proper ranges. All measures will be on the right side of the body to stay in accordance with ACSM guidelines. Computed Tomography (CT). Single Slice CT images (Siemens Definition) will be used to quantify skeletal muscle and fat area of the right and left thighs of each subject using 100mA with a scanning time of 3 s and a 512 X 512 matrix. With the subject supine, one 5-10 mm thick cross-section scan of both legs will be taken corresponding to the midpoint between the inguinal crease and the proximal border of the patella (the midthigh). Tissue area quantification will be determined using corresponding attenuation values of =200HU; -190 to -30 HU; and 0-100 HU for bone, adipose tissue, and skeletal muscle respectively using available software (NIH ImageJ; <http://rsbweb.nih.gov/ij/>). Total thigh fat will be further subdivided into two compartments including the fat above the fascia latae (subcutaneous thigh fat) and below the fascia latae (deep thigh fat). In addition, the skeletal muscle will be subdivided into areas of low attenuation (0-34 HU) representing fat rich muscle, and high attenuation values (35-100 HU) representing muscle with normal fat content. Images obtained as dicom files from UK Radiology will also be sent to the University of Arkansas Medical School and/or Central Arkansas Veterans Healthcare Administration for evaluation with another medical image analysis platform called sliceomatic. All images will be deidentified so that each subject will remain anonymous and only coded with their study identification number. Muscle biopsies. Three muscle biopsies (approximately 250 mg each) will be obtained from the vastus lateralis after local anesthetic (1% lidocaine) using a 5 mm Bergstrom needle with suction. As described above, there will be a baseline muscle biopsy, another at 2 weeks of drug/placebo treatment, and the final biopsy at 16 weeks. This procedure is routinely performed at both sites using the same processing method, with subjects returning for multiple biopsies. Muscle tissue will be divided as follows: 100 mg will be processed for myoblast isolation (Aim 3); ~100 mg will be snap frozen (~30 mg aliquots) in liquid nitrogen for RNA and protein isolation (Aim 2); and ~50 mg will be mounted in tragacanth gum and frozen in liquid nitrogen-cooled isopentane for detailed immunohistochemical (IHC) analyses (Aim 2), including myofiber CSA (Aim 1). Dietary monitoring. Participants will be asked to maintain their normal dietary intake throughout the study period. Energy intake and macronutrient composition will be assessed by 4 day diet records on each of the testing visits (Table 1). The nutrient content will be determined by those qualified to use the Nutrition Data System for Research, which utilizes the multiple-pass method to help improve the validity of dietary data 7. Randomization to Drug or Placebo. After informed consent and all tests to establish eligibility, participants will be randomized to receive either placebo or metformin treatment for 2 wk, followed by a 14 wk PRT program, with continued drug or placebo. Every effort will be made to conduct the randomization so that the metformin and placebo groups are equivalent. Since recruitment at UAB is expected to be more than at UK, participants will be stratified by site prior to randomization. Additionally, SPPB score will also be used for stratification. Randomization, stratified by site (UAB vs. UK) and by functional status (SPPB 3-8 vs. 9-12), will be implemented in permuted blocks of 4 using SAS v9.2 PROC PLAN to ensure adequate distribution of all groups across the collection period. In the event that other variables prove to be different between the two groups and have an impact on the outcome, covariate-adjusted analyses will be utilized as described below. Subjects randomized to metformin (850 mg each capsule) will take increasing doses as follows: 1 capsule (850 mg) per day for 7 days, 2 capsules per day (1700 mg) for 7 days, the latter being the target clinical dose, continued throughout the 14 wk of PRT. In some subjects, the dose progression may be slower and may not reach 1700 mg/day due to GI side effects. The placebo capsules will look identical to the metformin capsules, but will contain inert substances, and the escalating dose schedule will be the same. The metformin and placebo tablets will be obtained commercially through different facilities. The placebo tablets will be obtained from the VA Cooperative Studies Program Clinical Research Pharmacy Coordinating Center, which is in New Mexico (working through their non-profit foundation, the Biomedical Research Institute of New Mexico). This program is registered with the FDA as a manufacturing, packaging and distribution facility and serves the needs of VA studies, as well as NIH funded and some industry studies. We will contract with this facility to supply us with metformin placebos. There are many different manufacturers of metformin, and the VA facility in New Mexico will provide us with a tablet which will be identical to metformin 850 mg tablets that are manufactured by Amneal Pharmaceuticals, which is an established generic drug maker. Therefore, we will obtain placebo tablets from the New Mexico VA facility, and we will purchase generic (Amneal) 850 mg metformin tablets through our investigational pharmacy. Progressive resistance exercise training (PRT). The 14 weeks of PRT (42 sessions ± 3-5 sessions) will be supervised by trained personnel (exercise physiologists, or senior level physical therapy or athletic training graduate students under the supervision of an exercise physiologist). Each site has a certified, lead exercise physiologist with several years of experience, responsible for managing the day-to-day activities and supervising all trainers. Subjects will be instructed on proper techniques and continuously monitored. Following warm-up, PRT will consist of 8 constant load movements to train all major muscle groups (leg press, knee extension, one legged squat, calf press, chest press, lat pull down, biceps curl, and triceps pressdown). All resistance exercises will be performed bilaterally, progressing to reach full volume and intensity for each exercise by the end of wk 2. We will implement a variable intensity prescription: "high-low-high" 3 d/wk program. On Mondays and Fridays, intensity will be high – subjects will complete 3 sets of 8-12 repetitions at 70-75% 1-repetition maximum (1-RM) with 60-90s between sets. Progression will be incorporated continuously by incrementing the resistance load when 12

repetitions are completed for 2 of 3 sets. On Wednesdays, resistance loads will be reduced ~30% and the emphasis will be on more rapid, concentric training (with controlled eccentric loading) to develop explosive power while providing a protracted recovery period between high resistance sessions. Participants will aim to complete 42 exercise sessions but will have the flexibility to train  $\pm$ 3-5 sessions to account for follow up testing as well as for patient schedules and vacations etc. Participants should be in good compliance by completing at least 3 exercise sessions (high/low/high) in a row before follow up testing. Banking of samples. The consent form requests permission from subjects for banking of leftover samples for future research, to be kept indefinitely.

#### 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).

Research material obtained from patients will consist of a phone script, blood and muscle tissue samples, and the data resulting from biochemical analysis, DXA scans, functional/strength tests, and data derived from physical exams, diet records, and questionnaires.

#### 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.

The project is supported by an NIH RO1 grant and the PI's are Drs. Peterson, Kern, and Bamman (UAB). This is a dual site study where each PI brings complementary expertise so that in combination, all testing and analyses proposed can be performed expertly. They will communicate regularly to assure consistency in clinical assessments. Drs. Peterson, Bamman, and Kern have been working closely toward this trial for two years. At UK, this protocol will be performed at the CCTS, UK Medical Centers and KY Clinic, and the Human Performance Lab (HPL) located in the Multidisciplinary Sciences Building, Room B004. The HPL is outfitted with pneumatic resistance exercise training equipment, a Revolutionary Exerciser stationary bike (Keiser Sports Health Equipment, Fresno, CA) and a Biodex dynamometer for assessing strength, power and fatigue. The CCTS Clinical Operations unit comprises a research staff that is specially trained to make complex research observations and accurate patient assessments and documentation, to utilize precision in the collection and processing of specimens for research purposes, and to implement exemplary safe patient care practices. This unit is available to conduct research procedures for investigators throughout the institution or, under certain conditions, outside the institution and consists of both outpatient and inpatient units located on the third and fifth floors of the Chandler Medical Center respectively.

**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.

There are some potential risks associated with the procedures presented in this protocol. Resistance Exercise Training. The primary risks associated with resistance training are fatigue during exercise and muscle soreness or stiffness after exercise. There is a remote possibility of musculoskeletal injury resulting from resistance exercise. However, these symptoms are no different than what would normally result as part of any resistance exercise or strength training program and are both temporary and recoverable. Subjects may experience some temporary discomfort from exertion during exercise. Although this form of exercise is not a severe cardiovascular stress, there is a remote possibility of precipitation of angina or even a myocardial infarction in this population during resistance exercise. Metformin Treatment. Metformin is generally well-tolerated and causes few adverse side effects, the most

common being gastrointestinal upset, which is largely avoided by the proposed gradual dose escalation which reaches a maximum of 1700 mg/d gradually over the first 2 weeks. The most common side effect of metformin is diarrhea, which usually goes away with continued use, and which is mitigated by gradually increasing the dose. Very rarely, metformin can cause lactic acidosis, which can be severe. However, this is only associated with chronic renal insufficiency, and such patients (with creatinine > 1.4) will be excluded from the study. The study physicians are Endocrinologists who use metformin routinely in their clinical practice and are experienced in coaching patients in the use of metformin. Nevertheless, there are some patients who cannot tolerate metformin, or who cannot tolerate a significant dose. If a patient is experiencing difficulty with the drug, we will slow the pace of dose escalation. If a patient cannot take at least 850 mg/day, they will be dropped from the study. The placebo pills contain inert substances and no risks are foreseen. SPPB. The risks involved in motor control testing are minimal and involve the potential for falls. All participants may wear a gait belt around their waist and will be closely guarded during all physical performance testing. Two members of the research team will be present to minimize potential falls. Blood Draw. During venipuncture, there may be some slight discomfort experienced by the subject from the insertion of the needle into the vein. In addition, with needle insertion, potential infection, soreness, pain, bleeding, bruising, and fainting may occur. This pain and soreness may last up to 24 hrs following the procedure. OGTT. Subjects drink a standard 75 g glucose drink, followed by blood draws through a catheter over 2 hr. There is minimal risk or discomfort from this. Rarely a catheter inflammation/infection can occur. DXA and CT Scans. Radiation exposure from DXA and CT will be minimal. As a part of everyday living, everyone is exposed to naturally occurring background radiation, receiving a dose of about 200 to 300 millirem (mrem) each year. The effective dose from the set of the DXA X-ray procedures is about 1 mrem, comparable to one day of background radiation in Birmingham, AL or Lexington, KY. At this dose level, no harmful effects of radiation have been demonstrated and the risk is negligible. The single slice CT will impose approximately 22 mrem. Although the dose is small, accumulated radiation from medical x-rays can theoretically increase the risk of cancer. Muscle Biopsy. The investigators at both the UK and UAB sites have extensive experience with muscle biopsies. Based on our combined data from over 2500 percutaneous needle muscle biopsies using our routine protocol, the chance of infection is less than 0.4%, the chance of residual numbness around the biopsy site is less than 0.5%, the chance of bleeding/bruising beneath the skin is less than 0.5%, the chance of scarring of the muscle fascia is less than 0.2%, no incidence of deep muscle infection has occurred, and no allergic reaction to lidocaine was noted (participants are screened for lidocaine allergy). Subjects may experience some local soreness 6-48 hours after the biopsy. A small scar is likely to form but, in our experience, the scar typically fades and may not be detectable after several months. However, each subject is informed that if he/she is susceptible to keloid-type scar formation, the biopsy procedure may result in a permanent scar. Muscle Performance Testing. There is a remote possibility of musculoskeletal injury resulting from maximum strength and power testing. Subjects may experience fatigue, exertional discomfort, or delayed muscle soreness. From American College of Sports Medicine statistics based on maximal and submaximal exercise testing in both healthy and diseased populations, the risk of death is <0.01%, risk of myocardial infarction is <0.04%, and risk of complication requiring hospitalization is 0.1%. Other risks. In an older population with attendant chronic medical problems, there is always the possibility for unexpected events, and the medical staff will attend to these. These patients will likely be on other medications, and except for those mentioned above, these medications will not be changed. Exceptions include routine aspirin, which should be stopped 4 days prior to the muscle biopsy, and which may then be restarted 2 days later. If this medication cannot be stopped (eg. recent DVT, TIA, atrial fibrillation, stent, etc), then this patient cannot be part of the study. In our experience, patients who participate in studies often receive better medical care because of our attention to the details of their medications, medical problems, along with improved health through exercise. There are no foreseeable psychological, financial, legal, or other potential risks associated with the proposed research.

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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.

All procedures will be performed on each institution's CTSA, using skilled nursing, a hospital environment, and sterile procedures. Standard surgical practices ensure safety to the patients. No provision is made to compensate patients for any research related injury, and this is stated in the consent form. Privacy and Confidentiality. To protect confidentiality, all subjects are assigned a unique number, and this number is used for labeling of all samples and the identification of all laboratory material obtained from subjects, and there is no public release of the name of the subject from whom the material was derived. All data are kept in a password protected computer file (eg. Redcap) or in locked filing cabinets. All applicable HIPPA rules are followed, and all study personnel, including lab personnel, receive human subjects HIPPA training. As described below, this study will be monitored by a DSMB. Resistance Exercise Training. Exercise training volume and intensity will be progressively increased to avoid substantial soreness. All training sessions will be administered by highly experienced, certified (National Strength and Conditioning Association or American College of Sports Medicine) specialists with guidance from the PIs. Participants will have seated heart rate and blood pressure measurements taken before each session, and those with heart rate above 100 or less than 50 beats per minute, or blood pressure above 160/100, will not be allowed to exercise on that day. These issues will be evaluated by the study physician, and the participant may be referred to his/her primary care physician for further consultation. In case of an adverse event during any exercise testing session or procedure, personnel will have access to an AED located close by and will be trained in both CPR and AED. Emergency contact numbers will also be on hand. Metformin Treatment. Metformin is generally well-tolerated and causes few adverse side effects, the most common being gastrointestinal upset, which is largely avoided by the proposed dosing which reaches a maximum of 1700 mg/d. The most common side effect of metformin is diarrhea, which usually goes away with continued use, and which is mitigated by gradually increasing the dose. If a patient is experiencing difficulty with the drug, we will slow the pace of dose escalation. If a patient cannot take at least 850 mg/day, they will be dropped from the study. The risk of lactic acidosis will be avoided by excluding patients who are at risk for this rare complication. DXA and CT Scan. The effective radiation dose exposure cannot be avoided if muscle and fat mass are to be assessed. Muscle Biopsy. Muscle biopsies will be taken from the lateral portion of the vastus lateralis muscle using strict sterile procedures. Prior to taking the muscle biopsies, the skin will be aseptically cleaned with Betadine, and the skin and tissue

below will be injected with local anesthetic (1% lidocaine) to numb the area to pain. A small incision, about ¼ inch, will be made through the skin, through which a 5-mm Bergström type needle will be advanced into the muscle and suction applied. A piece of the muscle will be removed with the needle (~250-300 mg) and the skin closed with a single suture or steri strip. To minimize risk of bruising, a pressure dressing will be applied. These procedures will occur in the Clinical Research Units of the UAB and UK CTSA's with the full complement of nursing and medical personnel available. Risks associated with muscle biopsy will be minimized by the careful use of sterile procedures by a highly experienced team (e.g., at UAB Dr. Windham has performed over 1,000 biopsies for studies in collaboration with Dr. Bamman, and Dr. Kern has also performed over 1,000 biopsies). Muscle Performance and Mobility Function Testing. All testing sessions will be administered by highly experienced, certified (National Strength and Conditioning Association or American College of Sports Medicine) specialists with guidance from the PIs. Risks will be minimized by having at least 2 research staff members present during all testing and exercise training sessions. All invasive procedures will be performed by appropriately trained personnel under the supervision of the study physician. Subjects will be free to withdraw from the study for any reason.

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

The direct benefits to each participant include analyses of health and functional status, as well as body composition while enrolled in the study. The results of routine labs (lipids, OGTT, etc) will be provided to the patient as well as their physician. Participants will also benefit from supervised exercise training 3 d/wk for 14 wk, and are fully expected to benefit from the training program. On a larger scale, the results of this study will enhance our understanding of the effects of resistance training with and without adjuvant metformin treatment on muscle mass, strength, and function in older adults, and the impact of muscle inflammation susceptibility on outcomes. This information will markedly advance the field as a critical first step toward evidence-based, personalized exercise medicine. For these reasons, we consider the risks reasonable and the risk-to-benefit ratio for each participant to be low. This research will address three important knowledge gaps: (i) the role of muscle inflammation susceptibility on the blunted resistance training outcomes seen in some older adults; (ii) the efficacy of adjuvant metformin treatment; and (iii) whether effects of the combined treatment are mediated by M2 macrophages in muscle. With an interdisciplinary team of experts in geriatrics, exercise medicine, and muscle biology, we are poised to lead a paradigm shift in exercise prescription for older adults. We fully expect the novel findings to have an immediate and sustained impact on clinical practice and the development of personalized exercise medicine.

**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).

Participation in this study is strictly voluntary. There are no other alternative treatments, procedures, or choices for the subjects except for not to participate in the study. The subjects may however, decide to enroll in their own physical activity program outside of the program we are offering.

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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).

Research material obtained from patients will consist of blood and muscle tissue samples, and the data resulting from biochemical analysis, DXA scans, functional/strength tests, and data derived from physical exams, diet records, and questionnaires. For confidentiality and privacy, each subject will be given a study identification number and all data will be locked in a cabinets found within a locked office in Wethington and the HPL. Only approved study personnel will have access to the materials.

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

Provide a time table for destroying the data/specimens and identify how they will be destroyed, or provide rationale for perpetual maintenance [Note: The investigator is responsible for retaining the signed consent and assent documents and IRB research records for at least six years after study closure as outlined in the [Study Closure SOP](#) (PDF). If the research falls under the authority of FDA or other regulatory agency, the investigator is responsible for retaining the signed documents and IRB records for the period specified if

longer than six years after completion of the study]. For multi-site studies, the PI consults the study sponsor regarding retention requirements, but must maintain records for a minimum of six years after study closure. Also, specify who will access the identified data/specimens, and why they need access. If applicable, describe what measures will be taken to ensure that subject identifiers are not given to the investigator. If applicable, describe procedures for sharing data/specimens with entities not affiliated with UK.

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

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

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

If a research protocol involves the creation and/or use of a computer program or application, mobile or otherwise, please specify whether the program/application is being developed by a commercial software developer or the research team and provide any relevant information regarding the security and encryption standards used, how data is stored and/or transmitted to the research team, what information about the subjects the program/application will collect, etc. 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 appropriate protected.

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All data will be either stored in locked file cabinets and on secured password protected computer spreadsheets or within the core laboratories of the CCTS or Dr. Peterson. Each subject will be identified using only a study identification number and the investigators of this study will keep private all research records that identify the subjects. The information obtained from this research will be combined and presented in written materials, but these materials will not contain any subject identification. Only personnel associated with this study will have access to the data and to keep information confined, all subject information will be kept under lock and key in the research coordinator's office in 207E CT Wethington and/or in the HPL. All data will be kept for a period of six years after study closure. Data will be recorded using REDCap databases, supported through the CTAs. REDCap is a web-based, secure database tool with controlled access and regular backup. UK will be the data coordination site and both sites will enter data electronically using programmed edit checks to flag illogical or out-of-range values and skip patterns; data will be exported to SAS datasets. Both sites have CTA quality assessment/quality improvement programs; the QA/QI teams will perform quarterly audits to assure consistency between sites and good clinical practice. Identifiers may also be flagged so that private identifying information will not be exported.

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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.)

Due to the commitment required for the proposed studies, stipend payment is critical for subject recruitment, training, and completion of the study. However, the subjects will also derive significant benefits from participation in the exercise training program. Thus, minimal compensation of \$75 per subject is requested for those who participate in the initial testing phase of this project, and an additional \$225 per subject for those who participate in the 14 wk training program and post procedures for a total of \$300. Upon completion of the study or at time of withdrawal, participants will receive their payment for their time and effort.

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

There will be no costs to the research subjects. All procedures will be considered for research purposes.

**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. [i](#)

The proposed clinical trial will require IRB approval. Both sites have conducted similar trials in the past and are experienced with all regulatory requirements and with working with their IRBs. The PIs will be ultimately responsible for keeping all study documents updated and available for inspection by the sponsor, the UAB and UK IRBs, and other authorized reviewers. Both sites will report in the same manner and in the same timeframe. Monitoring for adverse events (AEs) will be conducted in real-time by the study investigators and study coordinators. Risks involved with this study are considered greater than minimal risk. For this reason, we will utilize the standing independent Data Safety Monitoring Board (DSMB) as chartered by the University of Kentucky Center for Clinical and Translational Sciences to monitor the safety of this study at both sites. The DSMB will review protocol performance, regulatory requirements, particularly the reporting of AEs, and will serve as the sole DSMB for the study. Both sites will use the same standardized AE report for the DSMB review to allow for an effective assessment of potential issues. The DSMB review will be given to the PIs and study coordinators who can then report to the UK and UAB IRBs during Continuation Reviews. The study coordinator will contact subjects within 48 hours of each procedure to assess for pain, infection, and other symptoms indicating possible post-procedure AEs. Subjects are discharged from the Clinical Research Unit with specific self-monitoring guidelines and instructed to call immediately for any concerning signs or symptoms. AEs will be graded according to intensity. 1=Mild: Complaint of discomfort noted but no disruption of normal daily activity. 2=Moderate: Discomfort sufficient to reduce or affect normal daily activity. 3=Severe: Incapacitating with inability to work or perform normal daily activity. The 5 point attribution scale for AE reporting will be used. 5=Definitely. 4=Probably. 3=Possibly; AE follows the procedure within a reasonable period, but may have been produced by the subject's clinical state or other factors (e.g. rash 7 days following the biopsy). 2=Probably not; AE does not follow the procedure or drug within a reasonable period and could readily have been produced by the subject's clinical state or other factors. 1= Definitely not; AE is judged to be clearly due to extraneous causes and does not meet the above criteria. Annual reporting of adverse events will be conducted with the IRB Continuation Review according to their protocol. These reports may also be forwarded to the DSMB. Serious AE (SAE) Reporting. Serious AEs will be reported to the IRB within 7 calendar days of the event. SAE's requiring prompt IRB reporting are defined as serious/life-threatening events involving risks to subjects or others and are unanticipated and are related to the study procedures. SAEs also include unanticipated or anticipated death related to the study procedures. The problem/adverse event may not fall under the IRB's prompt SAE reporting requirements as described above, but if in the PI's judgment, prompt reporting of the event(s) is in the best interest of the subject (s) because it may affect the safety and/or welfare of subjects and/or change the risk level of the study, the AE will be reported promptly. Data Accuracy and Protocol Compliance. All protocols involving human subjects will be directly supervised by the PI or her colleagues to assure compliance. All samples will be coded to eliminate bias. Detailed plans for maintaining subject confidentiality are described in the consent form. Interim results as well as any protocol violations can be seen in real time with the use of RedCap, an online password protected data entry portal. DSMB materials may also be shared at any time. Conflict of Interest. There is no conflict of interest. Investigators on this project have extensive experience with similar protocols and are well qualified to monitor progress and to determine what rate of unanticipated AEs is acceptable. For these reasons, Drs. Peterson and Kern and their colleagues are capable of monitoring for safety objectively and without bias.

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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.

All potential, current, and past subjects will be given three contact numbers in case any questions or complaints arrive. The research coordinator, Douglas Long, can be reached at 859-323-5438 or 614-313-4835. Further questions can be directed to the principal investigators, Dr. Charlotte Peterson, at 859-218-0476 or 859-619-6591 or Dr. Philip Kern at 859-218-1394 in case a resolution cannot be resolved at the coordinator level. Should a complaint arise, subjects will be asked to provide a written account of the complaint while the researchers will also provide their own account of the situation. All complaints will be collected, reported, and hand delivered to the IRB and 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](#)

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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](#). 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.



**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

**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 any use of a drug in a human other than the use of an approved drug in the course of medical practice?**

Yes  No

If yes, complete the questions below. Additional [study drug guidance](#).

LIST EACH DRUG INVOLVED IN STUDY IN THE SPACE BELOW

Drug Name:

Metformin

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	Form O- Investigational Drug.pdf

## STUDY DEVICE INFORMATION

### A DEVICE may be a:

- component, part, accessory;
- assay, reagent;
- software or computer/phone application;
- 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	Click applicable listing(s) for additional requirements and/or information:
<input type="checkbox"/> Academic Degree/Required Research <input checked="" type="checkbox"/> Aging Research <input type="checkbox"/> Alcohol Abuse Research <input type="checkbox"/> Cancer Research <input type="checkbox"/> Certificate of Confidentiality <input checked="" type="checkbox"/> CCTS-Center for Clinical & Translational Science <input checked="" type="checkbox"/> Clinical Research <input checked="" type="checkbox"/> Clinical Trial <input type="checkbox"/> Clinical Trial Multicenter(excluding NIH Cooperative Groups) <input type="checkbox"/> Clinical Trial NIH cooperative groups (i.e., SWOG, RTOG) <input checked="" type="checkbox"/> Clinical Trial Placebo Controlled Trial <input type="checkbox"/> Clinical Trial UK Only <input checked="" type="checkbox"/> Collection of Biological Specimens <input type="checkbox"/> Collection of Biological Specimens for Banking <input type="checkbox"/> Community-Based Participatory Research <input checked="" type="checkbox"/> Data & Safety Monitoring Board <input checked="" type="checkbox"/> Data & Safety Monitoring Plan <input type="checkbox"/> Deception <input type="checkbox"/> Drug/Substance Abuse Research <input type="checkbox"/> Educational/Student Records (e.g., GPA, test scores) <input type="checkbox"/> Emergency Use (Single Patient) <input type="checkbox"/> Genetic Research <input type="checkbox"/> Gene Transfer <input type="checkbox"/> GWAS (Genome-Wide Association Study) or NIH-funded study generating large scale genomic data <input type="checkbox"/> International Research <input type="checkbox"/> Internet Research <input type="checkbox"/> Planned Emergency Research Involving Waiver of Informed Consent <input type="checkbox"/> Pluripotent Stem Cell Research <input type="checkbox"/> Recombinant DNA <input type="checkbox"/> Survey Research <input type="checkbox"/> Transplants <input type="checkbox"/> Use of radioactive material, ionizing radiation, or x-rays [Radiation Safety Committee review required] <input type="checkbox"/> Vaccine Trials	<ul style="list-style-type: none"> <li>• <a href="#">Cancer Research (MCC PRMC)</a></li> <li>• <a href="#">Certificate of Confidentiality</a> (look up "Confidentiality/Privacy...")</li> <li>• <a href="#">CCTS (Center for Clinical and Translational Science)</a></li> <li>• <a href="#">Clinical Research</a> (look up "What is the definition of...")</li> <li>• <a href="#">Clinical Trial</a> (look up "What is the definition of...")</li> </ul> <p>Determine if research meets <a href="#">NIH definition of clinical trial</a>;            *Reminder: Ensure compliance with <a href="#">clinicaltrials.gov</a> registration requirements for applicable clinical trials and <a href="#">Good Clinical Practice (GCP) training</a> requirements.</p> <ul style="list-style-type: none"> <li>• <a href="#">Collection of Biological Specimens for Banking</a> (look up "Specimen/Tissue Collection...")</li> <li>• <a href="#">Collection of Biological Specimens</a> (look up "Specimen/Tissue Collection...")</li> <li>• <a href="#">Community-Based Participatory Research</a> (look up "Community-Engaged...")</li> <li>• <a href="#">Data &amp; Safety Monitoring Board</a></li> <li>• <a href="#">Data &amp; Safety Monitoring Plan</a></li> <li>• <a href="#">Deception*</a></li> </ul> <p>*For deception research, also go to the E-IRB Application Informed Consent section, checkmark and complete "Request for Waiver of Informed Consent Process"</p> <ul style="list-style-type: none"> <li>• <a href="#">Emergency Use (Single Patient) [attach Emergency Use Checklist]</a> (PDF)</li> <li>• <a href="#">Genetic Research</a> (look up "Specimen/Tissue Collection...")</li> <li>• <a href="#">Gene Transfer</a></li> <li>• <a href="#">HIV/AIDS Research</a> (look up "Reportable Diseases/Conditions")</li> <li>• <a href="#">Screening for Reportable Diseases [E2.0000]</a> (PDF)</li> <li>• <a href="#">International Research</a> (look up "International &amp; Non-English Speaking")</li> <li>• <a href="#">Planned Emergency Research Involving Waiver of Informed Consent*</a></li> </ul> <p>*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"</p> <ul style="list-style-type: none"> <li>• <a href="#">Use of radioactive material, ionizing radiation or x-rays for research</a></li> </ul>



**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. [i](#)

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:

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.):

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](#)

**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:

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 \(GME\)](#)

**\*\* 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

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".]

Attach Type	File Name
AdditionInfoConsiderations	CR 14-0330 Peterson for EIRB w DSMB 092418.pdf

**SIGNATURES (ASSURANCES)**

On all IRB applications there is a requirement for additional assurances by a Department Chairperson (or equivalent) [hereafter referred to as "Department Authorization"], and when applicable, a Faculty Advisor (or equivalent), which signifies the acceptance of certain responsibilities and that the science is meritorious and deserving of conduct in humans.

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

**Required Signatures:**

First Name	Last Name	Role	Department	Date Signed	
Charlotte	Peterson	Principal Investigator	Health Sciences - Rehabilitati	09/24/2018 12:50 PM	<a href="#">View/Sign</a>
Janice	Kuperstein	Department Authorization	Health Sciences - Rehabilitati	09/24/2018 11:55 AM	<a href="#">View/Sign</a>

**Principal Investigator's Assurance Statement**

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

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

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

- I have appropriate facilities and resources for conducting the study;
- I am aware of and take full responsibility for the accuracy of all materials submitted to the IRB for review;
- If applying for an exemption, I also certify that the only involvement of human subjects in this research study will be in the categories specified in the Protocol Type: Exemption Categories section.

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

**Department Authorization**

This is to certify that I have reviewed this research protocol and that I attest to the scientific validity and importance of this study; to the qualifications of the investigator(s) to conduct the project and their time available for the project; that facilities, equipment, and personnel are adequate to conduct the research; and that continued guidance will be provided as appropriate. When the principal investigator assumes a sponsor function, the investigator is knowledgeable of the

additional regulatory requirements of the sponsor and can comply with them.

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

**SUBMISSION INFORMATION**

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

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

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

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

Your protocol has been submitted.

	<b>Document Type</b>	<b>File Loaded</b>	<b>Document Description</b>	<b>File Size</b>	<b>Modified By</b>	<b>Mod Date</b>
⚡	Stamped Consent Form	Metformin IRB Approval 042516.pdf		0.712	jlsmit6	10/16/2018 10:19:47 AM
⚡	Stamped Consent Form	Form C with HIPAA- Metformin 040816 clean.pdf		0.267	jlsmit6	10/16/2018 10:19:47 AM
⚡	Stamped Consent Form	Initial Phone Screening Guide and Questionnaire Metformin- 060214 clean.pdf		0.125	jlsmit6	10/16/2018 10:19:47 AM
⚡	ApprovalLetter	ApprovalLetter.pdf		0.059	jlsmit6	10/16/2018 10:19:47 AM
⚡	AdditionInfoConsiderations	CR 14-0330 Peterson for EIRB w DSMB 092418.pdf	CR Peterson 092418 with DSMB	0.726	delong2	9/24/2018 11:48:27 AM
⚡	StudyDrug	Form O- Investigational Drug.pdf	Form O Investigational Drug	0.168	delong2	9/24/2018 11:15:12 AM
⚡	Advertising	REHAB-108_flyer3(PR).pdf	Flyer 3 with PR approval	0.373	delong2	9/24/2018 10:55:52 AM
⚡	Advertising	REHAB-108_flyer2(pr).pdf	Flyer 2 with PR approval	0.357	delong2	9/24/2018 10:55:34 AM
⚡	Advertising	REHAB-108_newspaper3x5APPROVED.pdf	Newspaper ad approved	0.309	delong2	9/24/2018 10:55:14 AM
⚡	Advertising	REHAB-108_spotlight22x28 (PR).pdf	Spotlight approved	4.244	delong2	9/24/2018 10:54:57 AM
⚡	Advertising	REHAB-108_flyer_RM(PR).pdf	FLyer for Research Match with PR approval	0.227	delong2	9/24/2018 10:54:28 AM
⚡	Advertising	REHAB-108_flyer_PR.pdf	FLYER 1 with PR approva1	0.302	delong2	9/24/2018 10:53:53 AM
⚡	StudyDesign	Form B- Metformin 031417 Clean.doc	Form B with Tables/Figures	0.142	delong2	9/24/2018 10:50:33 AM
⚡	Informed ConsentHIPAA Combined Form	Initial Phone Screening Guide and Questionnaire Metformin- 060214 clean.pdf	Phone Script IRB Approved	0.081	delong2	9/24/2018 10:36:48 AM
⚡	Informed ConsentHIPAA Combined Form	Form C with HIPAA- Metformin 040816 clean.pdf	Clean Informed Consent/HIPAA	0.147	delong2	9/24/2018 10:35:49 AM
⚡	Informed ConsentHIPAA Combined Form	Metformin IRB Approval 042516.pdf	Latest IRB Approved Consent/HIPAA	0.680	delong2	9/24/2018 10:29:07 AM

## Protocol Changes

Protocol Number: 47128

No Changes

There are no recorded changes tracked for this protocol.

## Study Personnel Changes:

No Changes

There are no recorded changes to study personnel.

No comments