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IRB Approval
6/11/2025
IRB # 70889
IRB2

IMPORTANT NOTE:

If you accidentally select the wrong IRB type or "Protocol Process Type" while your Initial Review (IR) application is in draft form (unsubmitted), you may change your selections. Please contact the Office of Research Integrity (ORI) at 859-257-9428, IRBsubmission@uky.edu, or request a consult to resolve any questions regarding your selections *prior* to submitting your Initial Review application.

If your **submitted IR application has been returned to you for requested revisions or additional information,** to streamline the review process **do not make changes** to your selections here **unless instructed to do so by the ORI/IRB.**

Changes to this section cannot be made after initial approval has been issued (the option is not available for MR or CR).

For guidance, see:

- Which IRB should review my research?
- Which Protocol Process Type?
- "Getting Started"

Which IRB

- (•) Medical ( ) NonMedical

Protocol Process Type

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

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

EXPEDITED CERTIFICATION

0 unresolved comment(s)

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(i)*

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 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 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.**

* Study must meet one of the IDE Exempt categories listed on the Device Form Attachment.
** An approved Device used in research according to its approved labeling is considered Exempt from IDE requirements.
NOTE: Select Category 1 for compassionate use medical device applications or individual patient expanded access investigational drug applications for which FDA has waived the requirement for full review.

☐ 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 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." 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 or will be collected solely for non-research purposes (such as medical treatment or diagnosis) as well as research involving existing information or specimens that were previously collected for research purposes, provided they were not collected for the currently proposed research. (Note: Some research in this category may qualify for Exempt review. This listing refers only to research that is not exempt.)
(Note: If submission includes materials previously collected for either non-research or research purposes in a protocol for which IRB approval expired, you may check Category 5. However, a separate category must also be selected for prospective collection of data/specimens obtained solely for research purposes)

☐ 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. This listing refers only to research that is not exempt.)

CONTINUATION REVIEW/FINAL REVIEW

0 unresolved comment(s)

In accordance with federal regulations and/or local policies, the IRB conducts periodic review of all currently approved projects. If you need your IRB approval to continue and you do not complete and submit the required materials in a timely manner, IRB approval will expire at the end of your current approval period.

If you have any questions, please contact the Office of Research Integrity at 859-257-9428 or email IRBsubmission@uky.edu.

To initiate your continuation review (CR)/annual administrative review (AAR), or properly close your study, complete this section and update/correct all other sections of your IRB application as applicable.
*****IMPORTANT*** Before leaving this page to update other sections of your application, be sure to SAVE this section first.**

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1. Status of the Research

Check the statement(s) that best describe(s) the current status of your research:

- ☐ No subjects have enrolled to date.
- ☐ Recruitment and/or enrollment of new subjects or review of records/specimens continue.
- ☐ Study is closed to enrollment, but subjects still receive research-related interventions (e.g., treatment, blood draws).
- ☐ Study enrollment is permanently closed; subjects have completed all research-related interventions; and the study remains active only for long-term follow-up of subjects (see Tool Tip above for info on long-term follow-up of subjects).*
- ☐ Research has progressed to the point that it involves 1) Data analysis, including analysis of identifiable private information or identifiable biospecimens; and/or 2) Accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care.*
- ☑ The remaining research activities are limited only to data analysis. There is access to records or specimens either directly or through codes or links to the data.*
- ☐ The remaining research activities are limited only to data analysis. There is no subject/record/specimen identifying codes or links to the data; the researcher or research team cannot readily ascertain the subject's identity.*
- ☐ All study activities are complete. IRB approval can be inactivated.

*Possibility that review will move from Full to Expedited.

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2. If subjects have been enrolled within the last year, and the IRB approved a consent/assent form for your study:

Please attach a complete, signed copy for the last two subjects enrolled with **each** consent/assent form/HIPAA form since the last annual review.
(Example: If 3 different approved consent forms were used since the last annual review, please provide the two most recent signed copies of each version for a total of six.)

Attachments

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3. Informed Consent

If the study is **open to subject enrollment, please go to the Informed Consent section of the E-IRB Application and verify attachment(s) include:**

- One clean copy in PDF (without the IRB Approval stamp) of the currently approved consent/assent document(s), or,
- If requesting changes to the consent/assent document(s), submit one copy with the changes highlighted (and designate Document Type as "Highlighted"), and one clean copy in PDF (without the changes highlighted).

If the study is **open to subject enrollment and the IRB has waived the requirement to document informed consent, please go to the Informed Consent section of the E-IRB Application and verify attachment(s) include:**

- One clean copy in PDF of the currently approved document used for the informed consent process (e.g., cover letter, phone script), or,
- If requesting changes to the consent/assent document(s), submit one copy with the changes highlighted (and designate Document Type as "Highlighted"), and one clean copy in PDF (without the changes highlighted).

If the study is **closed to subject enrollment, please go to the Informed Consent section of the E-IRB Application and remove Informed Consent Documents designated to get an IRB approval stamp to avoid having them appear valid for enrollment.**

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4. Unanticipated Problems Involving Risk to Subjects or Others/Adverse Events Summary & Assessment

Did any **problems/adverse events** occur during the last 12 months?

○ Yes ◉ No

In the space below, provide a written summary of both unanticipated problems* and available information regarding adverse events since the last review (e.g., initial review or annual/continuing review). The amount of detail provided in such a summary will vary depending on the type of research being conducted; in many cases, such a summary could be a brief statement that there have been no unanticipated problems and that adverse events have occurred at the expected frequency and level of severity as documented in the research protocol, the informed consent document, and investigator's brochure (if applicable). **The summary must include the PI's assessment whether the problems/adverse events warrant changes to the protocol, consent process, or risk/benefit ratio.**

Note: It is the IRB's expectation that all unanticipated problems involving risk to subjects or others or related deaths requiring prompt reporting are submitted in the appropriate time frame (See Policy [PDF]). Your response to this Annual/Continuing Review is considered assurance that all prompt reportable problems/adverse events have been submitted for IRB review.

*For multisite studies, the written summary should describe external events determined to be unanticipated problems involving risk to subjects or others.

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5. Subject Info To-Date

Our records for the previously approved IRB application indicate the **IRB approved estimate** of subjects to be enrolled (or records/specimens reviewed) is:

4

Enter the number of enrolled subjects (or records/specimens reviewed) that **have not been previously reported** to the IRB

0

Our records for the previously approved IRB application indicate the previous total # of subjects enrolled (or records/specimens reviewed) since activation of the study is:

4

The new total number of subjects enrolled (or records/specimens reviewed) since activation of the study:

4

Please review the Project Info section for the IRB approved estimate of subjects to be enrolled (or records/specimens reviewed). If this new total exceeds your approved estimate of subjects to be enrolled (or records/specimens reviewed), please update the number in the field for Number of Human Subjects in the Project Info section.

6. Data and Safety Monitoring Board (DSMB)/Plan (DSMP)

If your study is monitored by a DSMB or under a DSMP, attach all documentation (i.e. summary report; meeting minutes) representing Data and Safety Monitoring activities that have not been previously reported to the IRB.

Attachments

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7. Since the most recent IRB Initial/Continuation Review Approval:

Have there been any **participant complaints** regarding the research?

○ Yes ◉ No

If yes, in the field below, provide a summary describing the complaints.

Have any **subjects withdrawn** from the research voluntarily or by you as the PI for reasons related to safety, welfare, or problems related to the conduct of the research? If a participant does not meet the screening criteria for a study even if they signed a screening consent it is NOT considered a withdrawal.

○ Yes ◉ No

If yes, in the field below, provide a detailed explanation to the withdrawal(s) including if participants were lost to contact.

Has any **new and relevant literature** been published since the last IRB review, especially literature relating to risks associated with the research?

○ Yes ◉ No

If yes, attach a copy of the literature as well as a brief summary of the literature including, if pertinent, the impact of the findings on the protection of human subjects.

Attachments

Have there been any **interim findings?**

○ Yes ◉ No

If yes, attach a copy of **Interim Findings**.

Attachments

Have **subjects experienced any benefits?**

○ Yes ◉ No

If yes, in the field below, provide a description of benefits subjects have experienced.

Have there been any **inspections/audits/quality improvement reviews** of your research protocol resulting in the need for corrective action in order to protect the safety and welfare of subjects?

○ Yes ◉ No

If yes, please attach documentation evidencing the outcome(s) and any corrective action(s) taken as a result.

Attachments

Was an FDA 483 issued as a result of any inspections/audits?

○ Yes ◉ No

If yes, submit documentation using attachment button above.

8. Risk Level:

Our records for the previously approved IRB application show your research is:

Risk Level: **2**

Has something during the course of your research changed the level of risk?

◉ Yes ○ No

If yes, go to the Risk Level section, mark the appropriate risk level, and in the field below, describe why the risk level has changed:

Risk level changed to 1 because the study is closed to enrollment. We are analyzing data acuquired from the study

9. Funding/Support:

Our records for the **previously approved** IRB application indicate your research is being submitted to, supported by, or conducted in cooperation with the following external or internal agency(ies) or funding program(s):

☐ 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:

Please **update the Funding/Support section of your IRB application** if needed, including the following attachments if they contain changes not previously reported to the IRB:

- A current copy of your **protocol if you are conducting industry/pharmaceutical research;**
- A current **Investigator Brochure** (submit a copy with all changes underlined).
- A **new or revised grant application** for this project.

Did your project receive extramural funding?

○ Yes ◉ No

If yes, please review and correct if necessary, the OSPA Account # information under the **Funding/Support section** of your IRB application.

If the project is externally funded, has the sponsor offered any of the research team enrollment incentives or other personal benefit bonuses? (e.g., cash/check, travel reimbursements, gift checks, etc.)

○ Yes ○ No ◉ N/A

Note: It is University of Kentucky policy that personal benefit bonuses are not allowed. If these conditions change during the course of the study, please notify the IRB.

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10. Project Information

Our records for the previously approved IRB application indicate your estimated project end date is:

01/31/2024

If you have a new estimated project end date, please go to the Project Info section and change the date in the field for Anticipated Ending Date of Research Project.

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11. Study Personnel

Our records for the previously approved IRB application indicate the following individuals are study personnel on this project (if applicable):

Last Name	First Name
Adams Jr.	Thomas
Alcorn	Joseph
Bell	Robert

Last Name	First Name
Burris	Jessica
Christian	Amy
Garth	Patricia
Kahl	Joan
Means	Natalya
Rush	Craig
Shridas	Preetha

Please review the individuals listed above and update your records as needed in the Study Personnel section of the E-IRB application, being sure that each individual listed has completed or is up-to-date on the mandatory human research protection training [see the policy on Mandatory Human Subject Protection Training FAQs (required every three years)].

12. Progress of the Research

To meet federal requirements the IRB is relying on your RESEARCH DESCRIPTION as a protocol summary and their expectation is that it is up-to-date. If the currently approved protocol (or research description) in your E-IRB application is outdated, please make applicable changes, and describe in the field below any substantive changes and explain why they are essential. If none, insert "N/A" in the text field below. If you are closing your study, you may use the space below to summarize the final status of the research.

NA

Note: No changes in the research procedures should have occurred without previous IRB review. Approval from the IRB must be obtained before implementing any changes.

Provide a brief **summary** of any **modifications that affect subject safety and/or welfare** approved by the IRB since the last initial or continuation review (If none, insert "N/A" in the text field below.):

NA

Attach one copy of the most recent progress report sent to the FDA, if available. All PI-sponsored IND/IDE studies are required to submit a copy of the FDA progress report.

Attachments

13. Confidentiality/Security

Review your Research Description section and update the Confidentiality portion, if necessary, to describe measures for security of electronic and physical research records (e.g., informed consent document(s), HIPAA Authorization forms, sensitive or private data).

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14. Subject Demographics

Our records for the previously approved IRB application indicate the following categories of subjects and controls are included in your research:

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

Please review the Subject Demographics section of your IRB application for accuracy, and note the following:

If during the course of your research 1) any prisoners have been enrolled, OR 2) subjects have been enrolled that became involuntarily confined/detained in a penal institution that have not been previously reported to the IRB, go to Subject Demographic section in your E-IRB application and mark “prisoners” in the categories of subjects to be included in the study, if it is not already marked.

Note: If either 1 or 2 above apply, and you have received funding from the Department of Health and Human Services (HHS), a Certification Letter should have been submitted to the Office for Human Research Protections (OHRP); prisoners and individuals who have become involuntarily confined/detained in a penal institution cannot continue participation in the research until OHRP issues approval. If the Certification has not been submitted, contact the Office of Research Integrity.

Based on the **total # of subjects** who have enrolled, complete the subject demographic section below:

Participant Demographics

	Cisgender Man	Cisgender Woman	TGNB/TGE	Unknown/Not Reported
American Indian/Alaskan Native				
Asian				
Black or African American				
Latinx				
Native Hawaiian or Other Pacific Islander				
White	4			
American Arab/Middle Eastern/North African				
Indigenous People Around the World				
More than One Race				
Unknown or Not Reported				

If unknown, please explain why:

15. Research Sites

Our records for the previously approved IRB application indicate that you are conducting research at the following sites:

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 Schools/Education Institutions

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

Other Medical Facilities

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

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

Other:

If the above listed sites are not accurate, go to the Research Sites section of the E-IRB application to update the facilities at which research procedures have been or will be conducted.

If you are adding a new off-site facility, you may also need to update your E-IRB application Research Description, Research Sites, Informed Consent, and other affected sections as well as any documents which will list the off-site facility. Documents needing updating may include, but not limited to:

- Consent forms (attachment under Informed Consent section)
- Brochures (attachment under Additional Info section)
- Advertisements (attachment under Research Description section) ;
- Letter of support (attachment under Research Sites section)).

Please revise applicable sections and attachments as necessary.

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16. Disclosure of Significant Financial Interest

Disclosure of Significant Financial Interest:

Our records for the previously approved IRB application indicate that you, your investigators, and/or key personnel (KP) have a significant financial interest (SFI) related to your/their responsibilities at the University of Kentucky (that requires disclosure per the UK administrative regulation 7:2):

○ Yes ◉ No

If you need to update your records, please go to the PI Contact Information section and/or Details for individuals listed in the Study

Personnel section to change your response to the applicable question(s).

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17. Supplementals

To ensure the IRB has the most accurate information for your protocol you are expected to re-visit the E-IRB application sections and make corrections or updates as needed. At a minimum you are being asked to review the following sections for accuracy:

STUDY DRUG INFORMATION—Please review for accuracy.
STUDY DEVICE INFORMATION—Please review for accuracy.
RESEARCH ATTRIBUTES—Please review for accuracy.
OTHER REVIEW COMMITTEES -- Please review for accuracy.

PROJECT INFORMATION

0 unresolved comment(s)

Title of Project: (Use the exact title listed in the grant/contract application, if applicable).
If your research investigates any aspect of COVID-19, please include "COVID19" at the beginning of your Project Title and Short Title

Accelerated Transcranial Magnetic Stimulation (TMS) for Smoking Cessation in People Living with HIV/AIDS (PLWHA)

Short Title Description
Please use a few key words to easily identify your study - this text will be displayed in the Dashboard listing for your study.

Accelerated TMS for Smoking Cessation in PLWHA

Anticipated Ending Date of Research Project: 1/31/2024

Maximum number of human subjects (or records/specimens to be reviewed) 4

After approval, will the study be open to enrollment of new subjects or new data/specimen collection? ○ Yes ◉ No

Are you requesting that the UK IRB serve as the lead IRB for a multi-site study, **OR** that the UK IRB defer review to another IRB? [Click here for "IRB Reliance" help]

○ Yes ◉ No

If "Yes," before completing your IRB application, fill out the Reliance Request Form and submit it to irbreliance@uky.edu.

PI CONTACT INFORMATION

0 unresolved comment(s)

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*).

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 listed as PI here.

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.

The Principal Investigator's (PI) contact information is filled in automatically based on who logged in to create the application.

If you are not the Principal Investigator, do NOT add yourself as study personnel.
To change the PI contact information on an application in Researcher edit status:

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

  You will automatically be added as study personnel with editing permissions to continue editing the application.

Change Principal Investigator:

First Name:	Gopalkumar	Room# & Bldg:	Fountain Court
Last Name:	Rakesh	Speed Sort#:	40509
Middle Name			
Department:	Psychiatry - 7H800	Dept Code:	7H800
PI's Employee/Student ID#:	12461687	Rank:	Assistant Professor
PI's Telephone #:	857-222-2276	Degree:	MD
PI's e-mail address:	Gopalkumar.Rakesh@uky.edu	PI's FAX Number:	
PI is R.N.	○ Yes ◉ No	HSP Trained:	Yes
		HSP Trained Date:	9/15/2022
		RCR Trained:	Yes

Do you, the PI/researcher, 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

0 unresolved comment(s)

Indicate which of the categories listed below accurately describes this protocol

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

*"Minimal risk" means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves from those ordinarily encountered in daily life or during the performance of routine physical or psychological examination or tests.

*****For Expedited and Exempt Applications, the research activities must be Risk Level 1 (no more than minimal risk to human subjects).*****

Refer to UK's guidance document on assessing the research risk for additional information.

SUBJECT DEMOGRAPHICS **0 unresolved comment(s)**

Age level of human subjects: (i.e., 6 mths.; 2yrs., etc..) 18 to 60

Study Population:

Describe the characteristics of the subject population, including age range, gender, ethnic background and health status. Identify the criteria for inclusion and exclusion.

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;
- Justification for the inclusion of vulnerable groups such as children, prisoners, adults with impaired consent capacity, or others who may be vulnerable to coercion or undue influence.

Please consider this FDA Guidance on Enrollment of Participants from Underrepresented Populations in Clinical Studies

Inclusion criteria. Potential participants will be: 1) Patients enrolled in the Bluegrass Clinic; 2) 18-60 years of age; 3) male or female gender 4) Able to read, understand and communicate in English; 5) willing to adhere to the general rules of the Bluegrass Clinic/SMARTClinic/Beyond Birth Clinic; 6) willing and able to abstain from drug use other than Suboxone; 7) exhaled breath on day of study CO < 5 ppm; 8) Stabilized on maintenance buprenoprphine if having comorbid opioid use disorder.
Exclusion criteria. Positive pregnancy test for females, traumatic brain injury, history of seizure disorder, history of or current diagnosis of schizophrenia, intracranial metal shrapnel, previous adverse effect with TMS, sub-threshold consistency while performing behavioral tasks, failure to show baseline attentional bias to smoking versus neutral cues.
The main study is not connected to the Bluegrass HIV clinic, SMART clinic or the Beyond Birth Clinic. A person can be enrolled and receiving care at these clinics, and their participation in the research project does not impact their standing in any of these clinics. Participation is truly voluntary in nature.

To modify: A new updated phone script will be attached to this section.

Attachments

Attach Type	File Name
StudyPopulation	Phone Script_modified.doc

Indicate the targeted/planned enrollment of the following members of minority groups and their subpopulations. Possible demographic sources: Kentucky State Census, Kentucky Race/Ethnic Table, Kentucky Population Data.
(Please note: The IRB will expect this information to be reported at Continuation Review time for Pre-2019 FDA-regulated Expedited review and Full review applications):

Participant Demographics

	Cisgender Man	Cisgender Woman	TGNB/TGE	Unknown/Not Reported
American Indian/Alaskan Native:				
Asian:				
Black/African American:				
Latinx:				
Native Hawaiian/Pacific Islander:				
White:	4			
American Arab/Middle Eastern/North African:				
Indigenous People Around the World:				
More than One Race:				
Unknown or Not Reported:				

If unknown, please explain why:

Indicate the categories of subjects and controls to be included in the study. You may be required to complete additional forms depending on

the subject categories which apply to your research. If the study does not involve direct intervention or direct interaction with subjects, (e.g., record-review research, outcomes registries), do not check populations which the research does not specifically target. For example: a large record review of a diverse population may incidentally include a prisoner or an international citizen, but you should not check those categories if the focus of the study has nothing to do with that status.

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 Material
- ☐ Prisoners
- ☐ Non-English Speaking (translated long or short form)
- ☐ International Citizens
- ☐ Normal Volunteers
- ☐ Military Personnel and/or DoD Civilian Employees
- ☑ Patients
- ☐ Appalachian Population

ADDITIONAL INFORMATION:

Please visit the IRB Survival Handbook for more information on:

- Children/Emancipated Minors
- Students as Subjects
- Prisoners
- Impaired Consent Capacity Adults
- Economically or Educationally Disadvantaged Persons

Other Resources:

- UKMC Residents or House Officers [see requirement of GME]
- Non-English Speaking [see also the E-IRB Research Description section on this same topic]
- International Citizens [DoD SOP may apply]
- Military Personnel and/or DoD Civilian Employees

Assessment of the 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). If there is no direct intervention/interaction you will not need to answer the impaired consent capacity questions.

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

○ Yes ◉ No

If Yes and you are not filing for exemption certification, go to "Form T", complete the form, and attach it using the button below.

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

1 unresolved comment(s)

For creating 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 edit to match your research project.

Additional Resources:

- Informed Consent/Assent Website
- Waiver of Consent vs. Waiver of Signatures
- Sample Repository/Registry/Bank Consent Template

Consent/Assent Tips:

- If you have multiple consent documents, be sure to upload each individually (not all in a combined file).
- If another site is serving as the IRB for the project, attach the form as a “Reliance Consent Form” so the document will not receive a UK IRB approval stamp; the reviewing IRB will need to stamp the consent forms.
- 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
  - "Reliance Consent Form",
  - "Sponsor's Sample Consent Form".

How to Get the Section Check Mark

1. You must:

   a) provide a response in the text box below describing how investigators will obtain consent/assent, and
   b) check the box for at least one of the consent items and/or check mark one of the waivers

2. If applicable attach each corresponding document(s) **as a read-only PDF**.
3. If you no longer need a consent document approved (e.g., closed to enrollment), or, the consent document submitted does not need a stamp for enrolling subjects (e.g., umbrella study, or sub-study), only select "Stamped Consent Doc(s) Not Needed".
4. 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 and/or translated short form)
- ☐ Assent Form
- ☐ Cover Letter (for survey/questionnaire research)
- ☐ Phone Script
- ☐ Informed Consent/HIPAA Combined Form
- ☐ Debriefing and/or Permission to Use Data Form
- ☐ Reliance Consent Form
- ☐ Sponsor's sample consent form for Dept. of Health and Human Services (DHHS)-approved protocol
- ☑ Stamped Consent Doc(s) Not Needed

Attachments

Informed Consent Process:

Using active voice, in the text box below, describe how investigators will obtain consent/assent. Include:

- the circumstances under which consent will be sought and obtained
- the timing of the consent process (including any waiting period between providing information and obtaining consent)

- who will seek consent
- how you will minimize the possibility of coercion or undue influence
- the method used for documenting consent
- if applicable, who is authorized to provide permission or consent on behalf of the subject
- if applicable, specific instruments or techniques to assess and confirm potential subjects' understanding of the information

Will electronic consent form/process be utilized on-site or remotely for this study?

○ Yes ◉ No

If yes, in addition to addressing the above bullet points, describe the e-consent method and platform, including any hyperlinks, videos, or enhancements used to convey information, if applicable. Attach a representation of the e-consent with signature fields. For guidance, see the ORI E-Consent web page.

Note: all individuals authorized to obtain informed consent should be designated as such in the E-IRB "Study Personnel" section of this application.

Special considerations may include:

- Obtaining consent/assent for special populations such as children, prisoners, or people with impaired decisional capacity
- *Research Involving Emancipated Individuals*
  If you plan to enroll some or all prospective subjects as emancipated, consult with UK legal counsel **prior to submitting this application to the IRB**. Include research legal counsel's recommendations in the "Additional Information" section as a separate document.
- *Research Involving Non-English Speaking Subjects*
  For information on inclusion of non-English speaking subjects, or subjects from a foreign culture, see IRB Application Instructions for Recruiting Non-English Speaking Participants or Participants from a Foreign Culture.
- *Research Repositories*
  If the purpose of this submission is to establish a research repository describe the informed consent process. For guidance regarding consent issues, process approaches, and sample language see the Sample Repository/Registry/Bank Consent Template.

Informed consent will be obtained after thorough discussion of the research project for both the pilot study and the study proper, what is required of the participant, the risks and benefits of participation in the study, and the procedures that are in place if/when challenges arise. This will be done by the PI, one of the co-investigators or research assistant during the first encounter with the subject, if they fulfill all eligibility criteria and are interested in study participation.
The research project is not connected to the Bluegrass Care clinic/SMART clinic or Beyond Birth clinic. A person can be enrolled in these clinics and their participation in the research project does not impact their standing in the SMART clinic and therefore the participation is truly voluntary in nature.
If you have questions about the study, you can contact the principal investigator for the study Gopalkumar Rakesh at 857-222-2276. If you have concerns or questions about your rights and/or welfare as a volunteer in this research, you can contact the staff in the Office of Research Integrity at The University of Kentucky at (859) 257-9428 or toll free at 1-866-400-9428. We will give you a signed copy of this consent form to take with you

☐ Request for Waiver of Informed Consent Process

If you are requesting IRB approval to waive the requirement for the informed consent process, or to alter some or all of the elements of informed consent, 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 a waiver of the requirement for the informed consent process.

☐ I am requesting an 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.

Explain how each condition applies to your research.

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

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

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

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

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

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

☐ Request for Waiver of Signatures

If you are requesting IRB approval to waive the requirement for signatures on informed consent forms, **your research activities must fit into one of three regulatory options**:

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

Select the option below that best fits your study.

*If the IRB approves a waiver of signatures, participants must still be provided oral or written information about the study. To ensure you include required elements in your consent document, use the **Cover Letter Template** as a guide. There is an English and a Spanish version.*

○ **Option 1**

Describe how your study meets these criteria:

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

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

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

○ **Option 2**

Describe how your study meets these criteria:

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

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

○ **Option 3**

Describe how your study meets these criteria:

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

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

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

STUDY PERSONNEL **1 unresolved comment(s)**

Do you have study personnel who will be assisting with the research?
After selecting 'Yes' or 'No' you must click 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 required for a University of Kentucky academic program, the faculty advisor is also considered study personnel and should be listed below. ***Residents and students who are PI's are encouraged to designate the faculty advisor or at least one other individual as a contact with an editor role (DP).***
- Role: DP = Editor (individual can view, navigate, and edit the application for any review phase (IR, CR/FR, MR) or 'Other Review", and submit Other Reviews on behalf of the PI.)
- Role: SP = Reader (individual can view and navigate through the currently approved application only.)

To add an individual via the below feature:

- Search for personnel;
- Click "select" by the listing for the person you want to add;
- For each person, specify responsibility in the project, whether authorized to obtain informed consent, AND denote who should receive E-IRB notifications (contact status).

NOTE: Study personnel must complete human subject protection (HSP) and Responsible Conduct of Research (RCR) training before implementing any research procedures. For information about training requirements for study personnel, visit UK's HSP FAQ page, the RCR Home 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 (HSPTrainingSupport@uky.edu) for credit.

Study personnel assisting in research project:

Last Name	First Name	Responsibility In Project	Role	AC	Contact	Degree	StatusFlag	(HSP)	(HSP)Date	(RCR)	Removed?	Last Updated	SFI	Active
Adams Jr.	Thomas	Faculty Advisor	SP	Y	N		P	Y	08/18/2022	N	N	09/24/2021	N	Y
Alcorn	Joseph	Data Analysis/Processing	DP	Y	N	PhD	P	Y	03/13/2023	Y	N	09/24/2021	N	Y
Bell	Robert	Recruitment	SP	N	N		P	Y	01/16/2025	Y	N	07/10/2021	N	Y
Burris	Jessica	Recruitment	SP	Y	N		P	Y	06/03/2024	Y	N	07/17/2021	N	Y
Christian	Amy	Recruitment	SP	Y	N		P	Y	04/09/2024	Y	N	07/17/2021	N	Y
Garth	Patricia	Study Coordinator	SP	Y	N		P	Y	03/13/2023	Y	N	10/20/2022	N	Y
Kahl	Joan	Recruitment	SP	Y	N		P	Y	11/14/2023	N	N	07/17/2021	N	N
Means	Natalya	Recruitment	DP	Y	Y		P	Y	10/15/2024	Y	N	10/16/2023	N	Y
Rush	Craig	Co-Investigator	DP	Y	N	PhD	P	Y	08/16/2023	Y	N	01/04/2021	N	Y
Shridas	Preetha	Sub-Investigator	SP	N	N		P	Y	10/18/2023	Y	N	10/07/2023	N	Y
Anand	Pavan	Data Analysis/Processing	SP	N	N			Y	10/18/2022		Y	06/20/2024	N	N
Cordero	Patrick	Data Analysis/Processing	SP	Y	N	MD		Y	11/02/2022		Y	06/20/2024	N	N
Czerner-Garcia	Nicole	Project Assistance/Support	SP	Y	N		S	N	03/03/2022		Y	12/28/2022	N	Y
Elias	Madona	Data Analysis/Processing	DP	Y	Y		S	Y	07/18/2022	Y	Y	10/16/2023	N	Y
Gawthorp	Noah	Project Assistance/Support	SP	Y	N		P	N	05/26/2022		Y	04/25/2023	N	N
Himelhoch	Seth	Co-Investigator	DP	Y	N	MD MPH	P	Y	07/18/2022	N	Y	06/20/2024	N	Y
Jasinski	Lindsey	Faculty Advisor	SP	Y	N	PhD	P	Y	08/01/2023	Y	Y	10/20/2022	N	Y
Jenkins	Brooklyn	Project Assistance/Support	SP	Y	N		P	Y	02/02/2025	N	Y	04/25/2023	N	Y
Khanal	Rebika	Recruitment	SP	Y	N		P	N	02/04/2022	N	Y	06/20/2024	N	N
Sabitus	Kathryn	Consultant/Advisor	SP	Y	N		P	Y	06/21/2022		Y	10/20/2022	N	Y
Su	Amanda	Data Collection	SP	Y	N		P	N	06/02/2021		Y	10/20/2022	N	N
Thomas	Mareena	Project Assistance/Support	SP	Y	N		P	N	04/28/2022		Y	04/25/2023	N	Y
Thornton	Alice	Faculty Advisor	SP	N	N	MD	P	N	04/06/2022	N	Y	06/12/2025	N	Y
Wesley	Michael	Faculty Advisor	SP	Y	N	PhD	P	Y	11/07/2023	Y	Y	06/20/2024	N	Y

RESEARCH DESCRIPTION

0 unresolved comment(s)

You may attach a sponsor's protocol pages in the "Additional Information" section and refer to them where necessary in the Research Description. However, each prompt that applies to your study should contain at least a summary paragraph.

Pro Tips:

- **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 supplemental information with your application. During the document upload process, you will be able to provide a brief description of the attachment.**

Background

Include a brief review of existing literature in the area of your research. You should identify gaps in knowledge that should be addressed and explain how your research will address those gaps or contribute to existing knowledge in this area. For interventional research, search PubMed and ClinicalTrials.gov for duplicative ongoing and completed trials with same condition and intervention(s).

Importance of the Problem to Be Addressed. The proposed pilot study seeks to explore modulation of attentional bias and tobacco craving in PLWHA with one session of adequately dosed theta burst stimulation (TBS). Results of this trial will spur clinical research to further investigate the use of TBS as an adjunctive smoking cessation aid for PLWHA and could have broad implications for smoking cessation programs. Data obtained from this pilot study will also facilitate resubmission of a grant application examining adjunctive theta burst stimulation (TBS) combined with varenicline for smoking cessation in PLWHA. People living with HIV/AIDS (PLWHA) smoke at nearly three times the rate of the general population (1-7). These extraordinary smoking rates are associated with greater AIDS-related morbidity (8-10), non-AIDS related morbidity including non-AIDS-defining cancer, cardiovascular disease, pulmonary disease (11-18), and mortality (19-22). Smoking significantly impacts the progression and outcome of HIV disease and has been identified as the leading contributor to premature mortality in PLWHA (23). One study estimated PLWHA lose more years from smoking than from HIV infection (21). In our view, shared by others in the field, the single greatest health behavior change that could improve mortality is to assist smokers living with HIV/AIDS to quit smoking (23-30).

Pharmacotherapies for Smoking Cessation in PLWHA. Trials involving use of nicotine replacement therapy (NRT) have shown no effect on cessation rates when used alone (31, 32) and mild efficacy when used in combination with behavioral therapies in PLWHA (33-35). Adherence to NRT was also low (34). No controlled trials have compared NRT with other smoking cessation interventions in PLWHA (36). Although bupropion has been approved for smoking cessation in healthy adults, no randomized trials have explicitly examined the efficacy of bupropion for smoking cessation in PLWHA (36). There have also been concerns regarding interactions between bupropion and antiretroviral therapy (HAART)(37, 38). Varenicline is considered the most effective pharmacologic agent available for smoking cessation (39). There are no reported pharmacodynamic interactions between varenicline and HAART (37, 40). Varenicline was found to be safe and well tolerated for smoking cessation interventions among PLWHA (40-42). It showed higher continuous abstinence rates (OR=4.65, CI 1.71-12.67, p=0.003) compared to placebo during weeks 9-12 (43), when dosed for 12 weeks. In another trial combining varenicline and NRT resulted in significantly higher continuous abstinence at weeks 12 (OR=1.85, p=0.007) and 24 (OR=1.98, p=0.004) (44). Despite these results, suboptimal adherence to varenicline poses a significant barrier resulting in lower quit rates in community studies compared to clinical trials (45). The extant literature suggests the efficacy of pharmacotherapeutics prescribed as smoking cessations aids is suboptimal in smokers in general and PLWHA in particular (30, 36). These findings along with high smoking rates in PLWHA underscore the urgent need to identify novel adjuncts to augment the efficacy and sustainability of commonly prescribed pharmacotherapies for smoking cessation.

Transcranial magnetic stimulation (TMS). TMS is a form of noninvasive brain stimulation. TMS uses a magnetic field to generate tiny modulated doses of electric current at a focal brain site, leading to neural changes and consequently changes in behavior and illness symptoms (46). In psychiatric illnesses like major depressive disorder (MDD) and schizophrenia, TMS has been used to augment medication treatments or treat residual symptoms, which are addressed sub-optimally by pharmacotherapy (47, 48). TMS has revolutionized the treatment of major depressive disorder (MDD), leading to FDA approval in 2008 for 10 Hz protocol. Neuroimaging studies have shown neural effects from TMS to result from activity modulation at stimulation site and downstream effects at other brain regions (49). These downstream effects result from connectivity changes in networks involving proximal cortical stimulation target and distal network structures (49). TMS is safe and has been refined significantly over the last 20 years.

The neurobiology of nicotine addiction encompasses increased dopaminergic activity in the mesolimbic reward pathway (nucleus accumbens and ventral tegmental area), via removal of inhibitory GABAergic activity (50). TMS at the left dorsolateral prefrontal cortex (DLPFC) causes increased dopaminergic release at the site of application and downstream dopaminergic modulation in the reward pathway, consequently leading to reduced craving (51). A recent meta-analysis showed excitatory TMS to the left dorsolateral prefrontal cortex (DLPFC) showed a medium effect size for craving reduction for nicotine (Hedges' g 0.471, CI 0.820 to 0.122, p=0.008) (52). Importantly, across substances, including nicotine, number of stimulation pulses predicted the effect size for reductions in craving (52). TMS has been used for smoking cessation in a few clinical studies with otherwise healthy individuals (53). Ten previous studies have applied excitatory TMS (10-20 Hz), one study applied inhibitory TMS (1 Hz) and one previous study applied TBS to reduce craving for cigarettes in subjects with no comorbid psychiatric diagnoses (53). Number of sessions ranged from one to ten, with four being median (53). Eight studies targeted left or right DLPFC, one used an H coil targeting bilateral DLPFC and insula (54) and one study targeted the left superior frontal gyrus (55). Nine out of ten studies used craving measures as outcomes, all assessed abstinence from smoking cigarettes at various time points. All these have been pilot studies, with sample sizes ranging from 16 to 48.

Theta burst stimulation (TBS). A new TMS paradigm, theta burst stimulation (TBS), uses theta frequency stimulation nested within gamma frequency. TBS is different from other TMS frequencies in that it delivers significantly more dosing pulses over the same time period. TBS is safe and was approved for MDD by the FDA in 2019. To the best of our knowledge, there has been only a single clinical study that utilized theta burst stimulation for smoking cessation. Four sessions of intermittent TBS (iTBS) added to Cognitive Behavioral Therapy (CBT, twice weekly sessions for three weeks) (56) were delivered. Participants (N=74) received either iTBS (600 pulses) or sham TMS. The groups did not differ in number of cigarettes smoked or scores on Fagerstrom Test for Nicotine Dependence (FTND). At three months of follow-up, the iTBS group had 19 subjects reporting abstinence while 19 had relapsed. The sham TMS group had 10 subjects abstinent and 26 subjects who had relapsed. To the best of our knowledge, no studies used TBS or other rTMS for smoking cessation in PLWHA.

TMS for modulation of cognitive performance including attentional bias. TMS has also been used to modulate cognitive performance, to accelerate mechanisms of smoking cessation across various studies (57, 58). Previous TMS treatment studies for smoking cessation have included cognitive outcome measures including delayed discounting (59, 60) and cigarette cue induced craving assessed using an analogue scale (61). It is plausible modulation of these cognitive paradigms by TMS could contribute to craving reduction and behavioral changes in cigarette use. Multiple previous studies support the existence of an attentional bias towards smoking related cues compared to neutral cues in tobacco use disorder(62). Modulation of attentional bias has been attempted in MDD. To the best of our knowledge, no study has used TMS to modulate attentional bias in subjects with smoking behavior.

Stress induced craving paradigm. The pathophysiology of nicotine dependence includes the interaction between stress, environment and body physiology, fuelling the illness(63). Multiple previous studies have modeled craving for nicotine in the presence of stress, to approximate real world scenarios(64-66). Before we test TBS as a clinical intervention, we will explore whether one session of TBS can modulate craving in the context of induced stress. Two promising paradigms for stress induction are the cold pressor test (CPT) wherein participants immerse their feet in ice cold water (2-4 degree Celsius) for three minutes and the paced serial addition task (PASAT)(67). The cold pressor test invokes an immediate cardiovascular stress response, initiated by the sympathetic nervous system, followed by a neuroendocrine response controlled by the hypothalamus-pituitary-adrenal (HPA) axis(67). The PASAT is a cognitively challenging task and will be performed in parallel with the CPT as an additional means for stress induction. The task requires participants to listen to a standardized audio-recording of a series of single-digit numbers and to say aloud the sum of the last two numbers presented (within each inter-trial interval). The PASAT will also last less than three minutes. Peak stress response occurred 20 minutes after these paradigms were performed(67). In our pilot study, these paradigms will be performed simultaneously, and followed by the tobacco craving questionnaire (TCQ).

Brain network connecitivity to complement attentional bias modulation. Neuroimaging has shown resting state functional connectivity (rsFC) changes in patients who smoke(68). This encompasses connectivity changes in default mode network, executive control network and salience network. Previous studies have shown a negative correlation between smoking behavior severity and connectivity in the dorsal anterior cingulate (dACC)- ventral striatum (VS) circuit(68). Previous studies have also shown the salience network to be deeply involved in the regulation of attention to smoking cues versus neutral cues(68). Given that neuroimaging could potentially corroborate attentional bias modulation with TBS, we will attempt to explore correlations between changes in attentional bias and salience network as well as between changes in stress induced craving and connectivity in the dACC-VS circuit.

PLWHA who smoke cigarettes have lower resting heart rate variability (HRV) than people without HIV and people who do not smoke, respectively. Higher HRV is associated with better cardiovascular health and is negatively correlated with high sensitivity C-reactive protein (hs-CRP) which is a biomarker of inflammation. Consistent with this, resting HRV is lower for PLWHA who smoke than PLWHA who do not smoke.

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Objectives

List your research objectives. Please include a summary of intended research objectives in the box below.

To demonstrate whether four sessions of TBS improves attentional bias and craving in PLWHA smokers compared to four sessions of sham stimulation. We hypothesize 4 sessions of TBS to the left DLPFC will significantly improve attentional bias and craving for smoking cues compared to neutral cues in a population of subjects who are smokers with HIV/AIDS compared to sham stimulation.

Study Design

Describe and explain the study design (e.g., observational, secondary analysis, single/double blind, parallel, crossover, deception, etc.).

- *Clinical Research*: Indicate whether subjects will be randomized and whether subjects will receive any placebo.

- *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.
- *Qualitative research*: Indicate ranges where flexibility is needed, if a fixed interview transcript is not available, describe interview topics including the most sensitive potential questions.
- *Research Repositories*: If the purpose of this submission is to establish a Research Repository (bank, registry) and the material you plan to collect is already available from a commercial supplier, clinical lab, or established IRB approved research repository, provide scientific justification for establishing an additional repository collecting duplicate material. Describe the repository design and operating procedures. For relevant information to include, see the UK Research Biospecimen Bank Guidance or the UK Research Registry Guidance.

This will be a crossover randomized controlled trial. Recruitment for the study will be done by research assistant and/or principal investigator. All subjects will receive both TBS and sham stimulation in a randomized manner with counterbalancing. Subjects will be randomized to two groups - one group that receives actual TBS first and sham TMS later, the other group receiving sham TMS first and TBS later. The PI (Rakesh) will be blind to the randomization status and will supervise the TMS session. The PI will remain blind to the randomization status. Subjects will also remain blind to the randomization status. This will be facilitated by the Magventure Active/sham TMS coil which has been shown to maintain integrity of blinding in subjects regarding group assignment. We will recruit 30 subjects in each arm (2 arms – TBS and sham, total n=60), subjects will be randomized to one of these arms using a computer-generated randomization protocol.

On day one of the study, we will perform baseline assessments including breath alcohol level, opioid and tobacco craving questionnaires, smoking attentional bias tasks using eye tracker, inhibitory control and delay discounting tasks, collection of baseline demographics, vital signs (including heart rate, systolic and diastolic blood pressures), Snaith Hamilton Pleasure Scale and Hamilton depression rating scale. All of these baseline assessments will take a total of three hours. We will also obtain resting and active motor threshold from the first dorsal interosseous (FDI) muscle. Following this subjects will be transported to Magnetic Resonance Imaging and Spectroscopy Center (MRISC), affiliated with University of Kentucky for collection of their baseline MRI brain scan that will last thirty minutes. Subjects will also be escorted to the MRISC at the UK Medical Center by the PI (Rakesh) and a research assistant. Subsequently, neuroimaging data (MRI brain) will be acquired using a Siemens 3-Tesla (3T) PRISMA MRI scanner as described under Data Collection below.

On day two of the study will be the TMS session. We have two groups in this study, and you may be assigned to the actual TMS group or placebo by chance. If you are assigned to the actual TMS group, you will receive the intended experimental method of stimulation and dosing. The TMS paradigm we use is called theta burst stimulation (TBS) which is short and efficient TMS stimulation method. In this group, you will receive four sessions of actual TBS. In the placebo group, you will receive a different kind of stimulation which mimics the actual experimental one but does not deliver any electricity to the brain. This is called sham TMS and you will receive four sessions of it. In both groups, sessions will be separated by 50 minutes and during this time, you will perform a visual attention and a few scales to measure your craving for opioids and cigarettes. On day two we will also have you perform a stress test to assess craving for opioids and cigarettes. This would involve immersing your feet in cold water for three minutes while performing a number recall task. This will help us measure your craving for opioids and cigarettes more accurately than just doing the scales. At the end of day two, we will obtain an MRI brain scan.

This section will attach a schedule and lists of tasks that need to complete for four visits.

(Figure 1) will be attached to this section, incorporating all four visits details tasks. Timeline Tasks

Attachments

Attach Type	File Name
StudyDesign	(Figure 1) Timeline Tasks for four visits.docx
StudyDesign	Day_1_timeline_tasks.png
StudyDesign	Day_2_timeline_tasks.png
StudyDesign	Day3_timeline_tasks.png

Subject Recruitment Methods & Advertising

Describe how the study team will identify and recruit subjects. Please consider the following items and provide additional information as needed so that the IRB can follow each step of the recruitment process.

- How will the study team identify potential participants?
- Who will first contact the potential subjects, and how?
- Will you use advertisements? If so, how will you distribute those?
- How and where will the research team meet with potential participants?
- If applicable, describe proposed outreach programs for recruiting women, minorities, or disparate populations.
- How you will minimize undue influence in recruitment?
- Attach copies of all recruiting and advertising materials (emails, verbal scripts, flyers, posts, messages, etc.).

For additional information on recruiting and advertising:

- IRB Application Instructions - Advertisements
- PI Guide to Identification and Recruitment of Human Subjects for Research

We will recruit 60 subjects from the Bluegrass Care Clinic, SMART clinic and Beyond Birth Clinic. Study members will interface with all providers in these clinics on a daily basis. All providers in these clinics will be provided multiple copies of the business cards. All providers in these clinics will also be informed about inclusion and exclusion criteria for the study, based on which all patients will be screened by them. Initial contact will be made with potential subjects by those having legitimate access to the subjects' identities/information (ie only providers in the clinic). The PI (Dr Rakesh) and a research assistant will interface with a contact in each of these clinics on a daily basis. Business cards (that list a few study details and a call back number if subjects are interested in the study) will be provided to subjects at each of these clinics by clinic providers. The case manager for this clinic Robert Bell will send an email to all patients from the Bluegrass Care Clinic, with the business card attached and informing them about the study. A draft of the email is attached in the research procedure section. Subjects interested in the study can call the number provided on the business card to express interest in the study. This number belongs to the Patient Oriented and Population Science Shared Resource Facility (POP SRF). The POP SRF headed by Dr Burris will help the study team with phone screening subjects for the study and their recruitment if they fulfill inclusion and exclusion criteria. Members of the POP SRF (Jessica Burris, Joan Kahl and Amy Christian) have also been added to the list of key study personnel. The POP SRF works closely with Markey Cancer Center and they will assist the PI with recruitment. We are able to avail of this assistance since the study is funded by a pilot cancer center grant from Markey Cancer Center (MCC). Once a subject is identified as suitable for the study, the POP SRF will inform Dr Rakesh via UK email. Subjects will be asked to meet Dr Rakesh/research assistant either at MRISC or at 245 Fountain Court to get informed consent if they are interested in study participation and fulfill other eligibility criteria for the study. All data collected from phone screening would be entered into RedCap, regardless of whether subjects do or don't fulfill inclusion and exclusion criteria. During screening, subjects will not be coerced to participate in any way.
We have submitted an application to obtain a certificate Certificate of Confidentiality (CoC) for this study.
We will provide business cards having the study info to potential study subjects. This business card will display the contact number for the Patient Oriented and
Population Science Shared Resource Facility (POP SRF) 859- 218-6222 who will be involved in study recruitment.

To increase the UK clinic enrollment rate, we submit a stamped flyer by the CCTS for the UK-E-IRB review and approval.

Attachments

Attach Type	File Name
Advertising	70889-Updated Flyer-June-14-2022-STAMPED.pdf
Advertising	70889_business_card PR STAMPED.pdf

Research Procedures

Describe how the research will be conducted.

- What experience will study participants have?
- What will study participants be expected to do?
- How long will the study last?
- Outline the schedule and timing of study procedures.
- Provide visit-by-visit listing of all procedures that will take place.
- Identify all procedures that will be carried out with each group of participants.
- Describe deception and debrief procedures if deception is involved.

Differentiate between procedures that involve standard/routine clinical care and those that will be performed specifically for this research project. List medications that are explicitly forbidden or permitted during study participation.

On day one of the study, following informed consent, we will perform baseline assessments including breath alcohol level, opioid and tobacco craving questionnaires, smoking attentional bias tasks using eye tracker, inhibitory control and delay discounting tasks, collection of baseline demographics, vital signs (including heart rate, systolic and diastolic blood pressures), Snaith Hamilton Pleasure Scale and Hamilton depression rating scale. All of these baseline assessments will take a total of three hours. We will also obtain resting and active motor threshold from the first dorsal interosseous (FDI) muscle. Following this subjects will be transported to Magnetic Resonance Imaging and Spectroscopy Center (MRISC), affiliated with University of Kentucky for collection of their baseline MRI brain scan that will last thirty minutes. Subjects will also be escorted to the MRISC at the UK Medical Center by the PI (Rakesh) and a research assistant. Subsequently, neuroimaging data (MRI brain) will be acquired using a Siemens 3-Tesla (3T) PRISMA MRI scanner as described under Data Collection below. On the second and third days, subjects will receive either four sessions of active TBS or four sessions of sham stimulation. Subjects will receive all four sessions of either TBS or sham on one particular day, all four sessions will be the same in dosing and will be delivered at an interval of fifty minutes each. Each session will last ten minutes regardless of it being TBS or sham. Sessions will be delivered 120% resting motor threshold (RMT) to the left dorsolateral prefrontal cortex using a figure 8 coil and MagVenture MagPro x100 device (MagVenture A/S, Denmark), with TMS coil position stabilized using BrainSight (Rogue Solutions, Montreal, Canada). Deciding who will get TBS/sham sessions on day two will be done in a randomized manner with counterbalancing. Along with the stimulation, subjects will also perform a host of other tasks as shown in figures 1. Craving for cigarettes will be measured while performing a stress induction procedure involving immersion of feet in cold water coupled with performing a working memory task (cold pressor test and PASAT as described below). The figures also indicate the timing of these tasks. At the end of the stimulation sessions and tasks, post session MRI brain scans will be collected and subjects will be dispersed payments for the respective days.

On day two of the study will be the TMS session. We have two groups in this study, and you may be assigned to the actual TMS group or placebo by chance. If you are assigned to the actual TMS group, you will receive the intended experimental method of stimulation and dosing. The TMS paradigm we use is called theta burst stimulation (TBS) which is short and efficient TMS stimulation method. In this group, you will receive four sessions of actual TBS. In the placebo group, you will receive a different kind of stimulation which mimics the actual experimental one but does not deliver any electricity to the brain. This is called sham TMS and you will receive four sessions of it. In both groups, sessions will be separated by 50 minutes and during this time, you will perform a visual attention and a few scales to measure your craving for opioids and cigarettes. On day two we will also have you perform a stress test to assess craving for opioids and cigarettes. This would involve immersing your feet in cold water for three minutes while performing a number recall task. This will help us measure your craving for opioids and cigarettes more accurately than just doing the scales. At the end of day two, we will obtain an MRI brain scan.

Motor Threshold
Motor threshold (MT) is defined as the TMS pulse amplitude needed to elicit an EMG response of 50 μV peak-to-peak average amplitude in a target muscle. MT is the standard in the field for determining the intensity of TMS for everyone to reduce seizure risk. The MEP for the right first dorsal interosseus (FDI) will be measured with EMG. The scalp region producing the largest amplitude MEP will be identified. At that scalp location, we will determine the TMS intensity eliciting average MEP amplitude of 50 μV peak-to- peak in the first DI muscle using an amplitude titration procedure (at least 5/10 trials). Individual MT will be used to determine the intensity of theta burst stimulation for everyone, as recommended by safety guidelines.

TBS application
A magnetic coil will be placed on the scalp and held in place with frameless stereotaxic equipment, using a sophisticated method of coil placement that will coregister scalp positions directly onto an average brain template. This Frameless Stereotaxic System Brainsight offers real-time three-dimensional display of cortical localization as the TMS coil is moved across the scalp. This will be used for coil positioning. This system uses a programmed robot arm to precisely position the TMS coil, and maintain its position, within 1 mm of the brain target chosen. Earplugs will be worn to protect hearing and low-volume white noise will be played through TMS-compatible headphones to mask the sound of the coil clicks. The intensity of the stimulation will be 80% of active motor threshold as reported in a previous studies. The participant will be seated comfortably with headphones and earplugs to protect the subject's hearing.

Stress induced craving paradigm
The pathophysiology of nicotine dependence includes the interaction between stress, environment and body physiology. Multiple previous studies have modeled craving for nicotine in the presence of stress, to approximate real world scenarios. Before we test TBS as a clinical intervention, we will explore whether one session of TBS can modulate craving in the context of induced stress. Two promising paradigms for stress induction are the cold pressor test (CPT) wherein participants immerse their feet in ice cold water (2-4

degree Celsius) for three minutes and the paced serial addition task (PASAT). The cold pressor test invokes an immediate cardiovascular stress response, initiated by the sympathetic nervous system, followed by a neuroendocrine response controlled by the hypothalamus-pituitary-adrenal (HPA) axis. The PASAT is a cognitively challenging task and will be performed in parallel with the CPT as an additional means for stress induction. The task requires participants to listen to a standardized audio-recording of a series of single-digit numbers and to say aloud the sum of the last two numbers presented (within each inter-trial interval). The PASAT will also last about three minutes. Peak stress response occurred 20 minutes after these paradigms were performed. In our pilot study, these paradigms will be performed simultaneously, and followed by the tobacco craving questionnaire (TCQ).

The Tobacco Craving Questionnaire-short form (TCQ-SF)
It consists of 12 items rated on a visual analogue scale. The original Tobacco Craving Questionnaire (TCQ) is a valid and reliable 47-item self-report instrument that assesses tobacco craving in four dimensions: emotionality, expectancy, compulsivity, and purposefulness. The short form has been found to be as valid and reliable as the original version.

Attentional Bias task
We will measure attentional bias using a validated database of smoking and neutral cues and Tobii Pro Fusion 120 Hz eye tracker (Tobii Technology, Sweden). Smoking and neutral cues will be presented side-by-side on the screen for 1000?milliseconds. Eye tracking will record eye movements and fixation times for both cue types. Upon offset of the cues, a visual probe ('X') will appear on either the left or right side of the computer screen. Participants will be instructed to respond as quickly as possible to the probe. The primary dependent variable will be mean fixation time (milliseconds) calculated by summing the total fixation time for each cue type and then dividing by the total number of critical trials (i.e., 40). Reaction times to the visual probe will also be collected.

Attention bias behavioral activation (ABBA) task using go/no go
A modified cued go/no-go task is used as a measure of inhibitory control. The procedures and parameters for the attentional bias-behavioral activation (ABBA) task are identical to the traditional cued go/no-go task except that opiate-related images serve as go cues and neutral images serve as no-go cues. Opiate related images and neutral images that will be used for this task are attached below.

Delayed discounting task
Participants are presented a fixed set of 27 choices between smaller, immediate rewards (SIRs) and larger, delayed rewards (LDRs). Three trials of the task are presented, money versus money, money versus opiate reward, and opiate versus opiate reward in varying amounts and with varying time periods. The 27 choices in each of these trial types define ten ranges of discount rates, eight of which are bounded above and below and two of which represent the endpoints (choices of all 27 immediate rewards or all 27 delayed rewards). Based on participants' choices of the immediate reward across trials, each participant is assigned a k value corresponding to the geometric midpoint of one of the eight ranges or one of the two endpoint values. Each participant is assigned a k value that yields the highest proportion of choices consistent with that assignment. That is, for each participant we compute the proportion of that person's choices that were consistent with assignment to each of the 10 values of k defined by the questionnaire (bounded or unbounded), and the participant is assigned to the value that yields the highest consistency among his or her choices. The discount rate that yields the highest relative consistency across trials provides the best estimate of the participant's k value. When two or more values yielded equal consistency, the participant is assigned a value corresponding to the geometric mean of those values. The discounting rate (k) is estimated with nonlinear regression using Mazur's (1987) hyperbolic-decay model, vd = V/ (1+kd), where V is the value of a an outcome delayed by d days and vd is the value of the immediate outcome – a proportion of V subjectively discounted at "rate" k. Distributions of k-values transformed with the natural logarithm (ln) tend to be approximately normal.

Barratt impulsiveness scale (BIS-11) - The BIS-11 is a 30-item self-report questionnaire to assess impulsivity that has been validated in multiple studies and other languages.

Modification Request to the research procedures:

An additional two follow-up visits will be added to this study research procedure by the study Principal Investigator Dr. Gopalkumar. Rakesh. The research team will follow up with subjects at one-week and two-week intervals with a urine cotinine test (ACCUTEST urine cotinine tests from Janet Pharmacocal) and carbon monoxide testing using Smokerlyzer (Bedfont Scientific Limited). These two follow-up short visits 2-3 minutes will be performed in the SMART clinic lab space. The CUTEST cotinine assay is a qualitative test and indicates the presence or absence of cotinine. Cotinine is a metabolite of nicotine, and these measures will help assess abstinence from cigarette smoking in response to our intervention. The additional follow-up visit details will be incorporated into the informed consent form and in the E-IRB application for IRB further review and approval.

Modification Request to the research procedures:
We will record resting heart rate 4 times on study day 2 using EKG leads. We will record at baseline, after the stress induction paradigm, after first TMS session and after the 4th session. This will allow us to monitor heart rate variability changes in response to stress and TMS.

We will also draw blood samples (2 ml each in EDTA) on study days 1 and 2 at the CCTS outpatient clinic situated on 3rd floor of PAV H, to measure high sensitivity C-reactive protein (CRP). This assay will assess inflammatory status. The assay will be done by Dr Shridas who has been added as a co-investigator to the protocol.
Reference

Benowitz NL, Bernert JT, Foulds J, Hecht SS, Jacob P, Jarvis MJ, Joseph A, Oncken C, Piper ME. Biochemical Verification of Tobacco Use and Abstinence: 2019 Update. Nicotine Tob Res. 2020 Jun 12;22(7):1086-1097. doi: 10.1093/ntr/ntz132. PMID: 31570931; PMCID: PMC7882145.
https://pubmed.ncbi.nlm.nih.gov/31570931/

A new figure (Figure 1) will be attached to this section, incorporating all four visits details.

Attachments

Attach Type	File Name
ResearchProcedures	(Figure 1) Timeline Tasks for four visits.docx
ResearchProcedures	Bell Email_Clean.docx
ResearchProcedures	TAQ.PNG
ResearchProcedures	BIS.pdf
ResearchProcedures	TCQ.png
ResearchProcedures	TMSSideEffects.doc

Data Collection & Research Materials

In this section, please provide the following:

- Describe all sources or methods for obtaining research materials about or from living individuals (such as specimens, records, surveys, interviews, participant observation, etc.), and explain why this information is needed to conduct the study.
- For each source or method described, please list or attach all data to be collected (such as genetic information, interview scripts, survey tools, data collection forms for existing data, etc.).
- If you will conduct a record or chart review, list the beginning and end dates of the records you will view.

Motor Threshold
Eye tracking to measure attentional bias for smoking cues versus neutral cues
Delay discounting task
Attention bias behavioral activation (ABBA) task using go/no go
Barratt impulsiveness scale (BIS-11)
Tobacco Craving questionnaire (TCQ)
TMS Side effects scale
Treatment acceptability questionnaire (TAQ)
Resting state functional magnetic resonance imaging (fMRI)

Neuroimaging data will be acquired on a Siemens 3-Tesla (3T) PRISMA scanner. A high-resolution (1 cubic millimeter voxels) T1-weighted MP-RAGE structural image will be acquired for each subject. Functional images will be acquired using echo-planar imaging. Hyper-angulated volumes will be acquired with 37 ascending and interleaved slices at an angle 30-degrees to the anterior-posterior commissure to prevent OFC washout. Additional parameters will be similar to those used in other approved neuroimaging protocols in our lab (e.g., a repetition time (TR) of 2 seconds, echo time (TE) of 25 ms, a flip angle of 90 degrees, and functional voxels of size 3.4mm x 3.4mm x 4.0mm). Image preprocessing will be performed in statistical parametric mapping (SPM) 12 software using standard procedures (see Wesley et al., 2014). Data from functional scans will be treated similarly to fMRI data in previous studies (e.g., slice-timing corrected, head-motion corrected, warped into MNI standard space, re-sliced to 4 cubic millimeter voxels and smoothed with an 8mm full-width, half-maximum (FWHM) Gaussian kernel).

To modify: An additional two follow-up visits will be added to this study research procedure by the study Principal Investigator Dr. Gopalkumar. Rakesh. The research team will follow up with subjects at one-week and two-week intervals with a urine cotinine test (ACCUTEST urine cotinine tests from Janet Pharmacocal) and carbon monoxide testing using Smokerlyzer (Bedfont Scientific Limited). These will be performed in the SMART clinic lab space. The CUTEST cotinine assay is a qualitative test and indicates the presence or absence of cotinine. Cotinine is a metabolite of nicotine, and these measures will help assess abstinence from cigarette smoking in response to our intervention. The additional follow-up visit details will be incorporated into the informed consent form and in the E-IRB application for IRB further review and approval.

Attachments

Resources

Describe the availability of the resources and adequacy of the facilities that you will use to perform the research. Such resources may include:

- Staffing and personnel, in terms of availability, number, expertise, and experience;
- Computer or other technological resources, mobile or otherwise, required or created during the conduct of the research;
- Psychological, social, or medical services, including equipment needed to protect subjects, medical monitoring, ancillary care, or counseling or social support services that may be required because of research participation;
- Resources for communication with subjects, such as language translation/interpretation services.

The TMS Suite is housed within the department of psychiatry (245 Fountain Court, Lexington, Kentucky 40509) at the University of Kentucky, Lexington. Currently it encompasses one experimental room covering about 600 sq feet on the second floor. We are in the process of purchasing a a MagPro X100 stimulator (MagVenture Inc, Atlanta,GA) with booster option and active cooling. The room will also also equipped with a laptop and a chair to provide TMS. The device is capable of producing rTMS over a wide range of parameters such as paired-pulse, theta burst stimulation, and both monophasic and biphasic waveforms. The machine weighs 35 kg and the cart encompassing the machine weighs 16 kg. Dimensions of the machine are 210 x 530 x 400 mm. We are also in the process of purchasing a frameless stereotaxic system (Brainsight Frameless, Rogue Research, Montreal, QC, Canada) for co-

registration of TMS coil position on the scalp with underlying cortical anatomy on the individual subject's three-dimensionally rendered MRI scan.This permits navigation of the TMS coil to target cortical structures. Participants are administered TMS in a customized chair for stabilization of head and coil position. A coil holder especially designed for TMS ensures stable coil positioning. The Brainsight Neuronavigation system has three main components: (1) NDI Spectra infrared camera system, (2) stimulator, (3) chair with neck rest. The TMS coil is targeted to a user defined location selected on the individual 3-D Anatomical MRI with fMRI or PET data overlay with less than one millimeter error. The TMS coil is attached to a stimulator unit, which administers the TMS pulses to modulate brain function in a spatially and temporally precise fashion. The subject reclines in the chair and wears a headband equipped with a subject position tracker. The ceiling mounted infrared stereo camera detects the 3-D position of the subject tracker and also the coil position tracker, and continuously feeds this information into the control center software.

Eye Tracker. The Tobii Pro Fusion housed at 245 Fountain Court is an exceptionally flexible remote eye tracking system offering supreme tracking performance in a wide array of human behavior research studies. This small eye tracking research system offers unprecedented portability and freedom of head movement in combination with unparalleled tracking accuracy and robust participant tracking capability. It allows for both screen and real-world test scenarios. For screen based research, it can be used with a laptop, an external monitor or an all-in-one PC. It can be mounted below most screens. With the eye tracker flush mounted on a screen, researchers can achieve highly accurate results for stimuli presentation on screens. Using a desk stand, one can track larger screens. This gives researchers the freedom to present stimuli on a screen that best meets the specific needs of the study at hand. The eye tracking system captures data up to speeds of 250 Hz (available 60, 120, 250 Hz modes). It delivers unparalleled data accuracy within the whole tracking box and very robust participant tracking capability. Robust eye tracking capability ensures very low data loss in real life conditions. The system with automatic selection of bright or dark pupil eye tracking accommodates for large variations in experimental conditions and demographic populations. The system also comes fitted with Tobii Pro Lab. This is a versatile biometric software platform designed for extensive research into human behavior using eye tracking analysis. It also has added ability to be combined with other physiological data streams. From in-store shopper research to psychology experiments, Pro Lab makes it easy for anyone to start using various biometric tools in their research in order to further expand the scope and richness of their insights. Pro Lab works well with both screen-based and wearable eye trackers.

Magnetic Resonance Imaging and Spectroscopy Center (MRISC). The Magnetic Resonance Imaging and Spectroscopy Center (MRISC) is a service and consultation center supporting basic and clinical research at the University of Kentucky. The Center includes an advanced 3T Siemens PRISMA scanner with high performance gradients, echo-planar whole body imaging and hydrogen spectroscopic capabilities for both human and animal studies. For dedicated animal studies, a modern Bruker/Siemens 7T MR scanner has recently been installed. Recently renovated facilities for animal handling, preparation and care are available immediately adjacent to the 7T imager. There are also computing facilities, electronic and fabrication shops, and a multi-user laboratory available to support magnetic resonance and spectroscopy studies. Scientific and technical personnel are available to help in developing MR sequences and procedures as well as to help with image-processing analysis. The Center has multiple ongoing research trials https://www.research.uky.edu/magnetic-resonance-imaging-and-spectroscopy-center/human-research-projects.

In 2017 the MRISC was awarded an NIH grant to upgrade its human MRI scanner from a Siemens TIM TRIO 3T to a Siemens MAGNETOM Prisma 3T. The Prisma 3T offers maximum performance under prolonged high-strain conditions and delivers improved resolution over the previous system by coils with the highest gradient strength currently available on the market. Of note, data collected with the Prisma 3T scanner are to a higher-quality standard and are therefore more attractive for inclusion into NIH-supported neuroimaging repositories, such as the Neuroimaging Informatics Tools and Resources Clearinghouse (NITRC) and the Human Connectome Project (HCP). The Prisma 3T is equipped with a full complement of coils, updated image processing using Siemens Software 3D rendering, image fusion, perfusion, DTI fiber tracking, spectroscopy, volume rendering, shaded surface display, multiplanar reconstruction, and maximum intensity projection.
Ancillary Equipment in MRI Suite. 1) Applied Sciences Laboratories, Inc. Model 504LRO (long range optics) eye tracker complete with Real Eye software; 2) AVOTEC, Inc. Silent Vision SL-6011 LCD projection system used with Psychology Software Tools, Inc. visual presentation software, EPRIME; 3) MRA, Inc. 10 channel, fiber optic, patient response system with trigger interface and visual/auditory patient monitoring; 4) Current Designs, Inc. patient response fORP Interface Unit with 12 fiber optic cables and an MRI compatible, handheld, trackball mouse; 5) Medrad, Inc. SHS200 Power Injector; 6) InVivo Research, Inc. Precess MRI compatible patient monitor with wireless digital SPO2, ETC02, heart rate and blood pressure recording; 7) Full suite of physiological monitoring equipment from S.A. INC for small animal imaging; and 8) Microcapstar Capnograph CO2 Analyzer and MRI-1ventilator from CWE instruments for small and medium sized animals.
Computing and Data Management. The following centralized computer and file server equipment is located in the MRISC and available (1) Server, Linux, 4U Rack mounted Dell PowerEdge 6850, 64bit - 4 Quad Core Xeon Tulsa, 16GB RAM, 1.5TB SAS RAID 5 array; (2) Two Disk Array, 3U Rack mounted Dell MD1000 Power Vault, 4.5TB SAS RAID 5 array; (3) Tape Backup, 2U Rack mounted Dell TL2000, 24 x 800GB/1.6TB cartridges; (4) Network Attached Storage (NAS), 1U Rack mounted NetGear, 2.0 TB SATA RAID 5 array; (5) Dell full size 4210 rack (42U slots total; 16U slots occupied including APC; 26U slots available).
All computers and servers are protected with power supply backup and surge protecting UPSs. All MRI scans are sent to the NAS backup server immediately after the imaging session and burned to CD for permanent archiving. The MRI scanner host computer is connected to the Dell rack, containing equipment items 1-4, by 1 GB/sec fiber optic cable while the rest of the computers are connected by Cat 5e cable on a 100 MB/sec network. Institution-wide upgrades to Cat 6a network cable are currently underway. Daily incremental tape backups are made from all data on all the servers, the NAS, and the MD1000 using Yosemite Backup software running on the Poweredge 6850. Full monthly tape backups are made and stored offsite. All computers and servers are behind the UK Medical Center firewall, have individual firewalls, are accessible only with valid usernames and passwords, and have automated operating system software updating.

Bluegrass Care Clinic for HIV. The Bluegrass Care Clinic, located in Lexington, Kentucky provides HIV care, case management and psychiatric services for PLWHA in the north central Kentucky region. Currently, the clinic provides care to 1700 unique PLWHA. Approximately 175 new unique clients enroll in the clinic each year. Seventy percent of people receiving care at the Bluegrass Clinic self-report smoking cigarettes, 97% receive a prescription for anti-retroviral medication and 93% remain virally suppressed. In the

Bluegrass Care Clinic there are approximately 1073 unique PLWHA, engaged in care who smoke. If we conservatively assume 1/2 may be ineligible for the study or chose not participate in the study, there are still over 500 eligible people to recruit for the study. This is nearly 2.5 times the number of people we would need to recruit (n=240) over the course of five years of the grant, if funded. These patients identify as male (81%), (18%) and transgender (1%).

The Supportive Medication Assisted Recovery Program (SMART) aims to comprehensively assess evaluation and treatment needs of patients with substance use disorders. It is housed at 245 Fountain Court and associated with the University of Kentucky. This clinic provides pharmacotherapy and psychotherapy treatment options for these patients in addition to urine drug screens and breathalyzer tests. Having 2 full time psychiatrists, 1 psychologists and 2 social workers on all days of the week, the clinic seeks to become a leader in integrative care in the state of Kentucky.

Potential Risks & Benefits

Risks

- Describe any potential risks – including physical, psychological, social, legal, ability to re-identify subjects, or other risks. Assess the seriousness and likelihood of each risk.
- Which risks may affect a subject's willingness to participate in the study?
- Describe likely adverse effects of drugs, biologics, devices or procedures participants may encounter while in the study.
- *Qualitative research* - describe ethical issues that could arise while conducting research in the field and strategies you may use to handle those situations.
- Describe any steps to mitigate these risks.

Benefits

- Describe potential direct benefits to study participants – including diagnostic or therapeutic, physical, psychological or emotional, learning benefits. This cannot include incentives or payments.
- State if there are no direct benefits.
- Describe potential benefits to society and/or general knowledge to be gained.

Describe why potential benefits are reasonable in relation to potential risks. If applicable, justify why risks to vulnerable subjects are reasonable to potential benefits.

Seizure is a theoretical risk with TMS. In the Rossi et al. report it was stated that "The occurrence of seizures has been extremely rare, with most of the few new cases receiving rTMS protocols exceeding previous guidelines, often in patients under treatment with drugs which potentially lowered the seizure threshold." As Rossi et al. delineate, "rare" means that 16 cases (out of tens of thousands of rTMS sessions over the last two decades) of seizure related to rTMS have been reported. Eight occurred before safety parameters were established in 1997. Of the other eight reports, six occurred either when the safe rTMS parameters were exceeded or other safety guidelines ignored, and the actual occurrence of a seizure has been questioned in the other two (i.e., convulsive syncope or pseudoseizure may have occurred). In a workshop convened by the National Institute for Neurological Disorders and Stroke (NINDS) in 1996, researchers in the field agreed upon a set of rTMS consensus safety guidelines, including recommended stimulation parameters and contra-indications, and these consensus guidelines have been recently updated (Rossi et al., 2009). Widespread adherence to the 1996 guidelines has resulted in the virtual elimination of inadvertent seizures in rTMS studies (Rossi et al., 2009). Theta burst stimulation (TBS) that we will use in this study has been documented to be extremely safe. The risk of seizure with TBS is 0.1% (Rachid, 2017). There has been only one seizure instance reported with continuous TBS in a subject with no previous history of epilepsy but was sleep deprived after a long flight (Oberman and Pascual-Leone, 2009).

The most commonly reported side effect of rTMS is headache. This headache is typically of a muscle-tension type. It usually develops during or immediately after the stimulation and may last for minutes to hours following the end of the stimulation. It is typically limited to the day of stimulation, and usually responds promptly to single doses of over the counter pain medications. Neck pain or scalp pain may also occur. Both are usually managed easily with over-the-counter analgesics.

As noted in Rossi et al. (2009), Loo and colleagues reported mild and transient changes in auditory threshold in two depressed patients following a 2-4 week rTMS course of rTMS (16). Cases of tinnitus have been reported after rTMS treatments. In addition, recently in a study investigating the effects of rTMS on symptoms of depression, a patient experienced moderate to severe tinnitus after an rTMS session in which earplugs were not used. Rossi et al. recommended that hearing protection always should be worn during rTMS application, and that individuals with cochlear implants not receive rTMS. In the current study, earplugs will be worn by all subjects during rTMS procedures. Individuals with cochlear implants will be excluded from participation.

Risks to the unborn children of pregnant women receiving rTMS are unknown. Pregnant women will be excluded in this study. If sexually active, the subject must agree to use appropriate contraceptive measures for the duration of the study. Medically acceptable contraceptives include: (1) surgical sterilization (such as a tubal ligation or hysterectomy), (2) approved hormonal contraceptives (such as birth control pills, patches, implants or injections), (3) barrier methods (such as a condom or diaphragm) used with spermicide, or (4) an intrauterine device (IUD). Contraceptive measures such as Plan B (TM), sold for emergency use after unprotected sex, are not acceptable methods for routine use. If the subject has any uncertainty about whether they could be pregnant, another urine pregnancy test will be performed before they can participate in this protocol.

The EKG leads can cause an allergic reaction causing your skin to become red at its point of contact with your wrist. We will remove the leads if you develop itching or skin redness at the site of application. The possible risks associated with blood drawing are pain, bleeding, fainting, bruising, infection and/or hematoma (blood clot under the skin) at the injection site. Since the blood draws will occur

at the CCTS outpatient clinic at PAV H of A.B. Chandler Hospital, we can avail specialized services if needed.

Other plausible risks include breach of confidentiality, development of suicidal thoughts and syncope (neurocardiogenic in nature). Vasodepressor (neurocardiogenic) syncope is a common reaction to anxiety and psycho-physical discomfort. It is a common experience that may occur more often than epileptic seizures during TMS testing and treatment. Suicidal thoughts have been observed to transiently develop only in subjects who have a previous history of major depressive disorder.

References pertinent to this section
Rossi S, Hallett M, Rossini PM, Pascual-Leone A, Safety of TMSCG. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol. 2009;120(12):2008-39.
Rachid F. Safety and Efficacy of Theta-Burst Stimulation in the Treatment of Psychiatric Disorders: A Review of the Literature. J Nerv Ment Dis. 2017;205(11):823-39.
Oberman LM, Pascual-Leone A. Report of seizure induced by continuous theta burst stimulation. Brain Stimul. 2009;2(4):246-7.
The study proper may benefit subjects in smoking cessation. It will also help us learn how TMS affects cognitive functions, visual attention, craving and impulsivity in people living with HIV who smoke. There are no known long-term health risks to the use of rTMS per se when operated within consensus safety guidelines (Rossi 2009). In 2008, the FDA approved the use of high frequency rTMS in the treatment of depression. Also in 2008, an international consensus conference on safety guidelines for rTMS (1) systematically reviewed the thousands of healthy subjects and patients who have undergone rTMS in order to allow for a better assessment of relative risks. The relative infrequency of adverse events using rTMS was noted. They concluded that in the case of Class 3 studies (studies involving indirect benefit and low risk in normal subjects and patients that are expected to yield important data on brain physiology or safety, but have no immediate relevance to clinical problems), normal volunteers should be permitted to participate in rTMS research when it is likely to produce data that are of outstanding scientific or clinical value. They also concluded that this research can be performed in a non-medical setting (i.e., psychology labs, robotics labs, research institutions, etc. as opposed to a hospital or appropriately equipped outpatient clinic). The Rossi et al. consensus report went on to suggest safety guidelines based on the now rather extensive international experience with rTMS. These guidelines include the rTMS intensity and timing parameters considered safe, training, and planning for and managing emergencies. We will follow these guidelines, and have incorporated them into our screening and session procedures.

Participation in the pilot and main parts for the study is completely voluntary, and there will be no pressure or time constraints regarding the decision to participate. If subjects experience headaches, they can withdraw without any ramifications pertaining to their respective clinic. There are no benefits to the participants except for the compensation, as well as the good will of helping the progress of scientific research. The information learned from this study may aid our understanding of the role of the TMS in modulating cognition and brain function in patients HIV and tobacco use disorder.

Rossi S, Hallett M, Rossini PM, Pascual-Leone A, Safety of TMSCG. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol. 2009;120(12):2008-39.

Available Alternative Opportunities/Treatments

Describe alternative treatments or opportunities that might be available to those who choose not to participate in the study, and which offer the subject equal or greater advantages. If applicable, this should include a discussion of the current standard of care treatment(s).

There are no alternative treatments suggested in this study

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Records, Privacy, and Confidentiality

Specify where the data and/or specimens will be stored and how the researcher will ensure the privacy and confidentiality of both. Specify who will have access to the data/specimens and why they need access.

Describe how data will be managed after the study is complete:

- If data/specimens will be maintained, specify whether identifiers will be removed from the maintained information/material.
- If identifiers will not be removed, provide justification for retaining them and describe how you will protect confidentiality.
- If the data/specimens will be destroyed, verify that this will not violate retention policies and will adhere to applicable facility requirements.

If this study will use de-identified data from another source, 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 collaborators not affiliated with UK.

For additional considerations:
Return of Research Results or Incidental Research Findings
HIPAA policies
FERPA policies
Procedures for Transfer agreements
Information regarding multi-site studies
NIH Genomic Data Sharing (GDS) Policy

Digital Data

Personal information of participants (Subjects' age, comorbid medical or psychiatric illnesses, history of substance use, history of traumatic brain injury/loss of consciousness, previous adverse effects with TMS, medication history, duration of treatment with suboxone, urine drug screens, breathalyzer test results) will be stored in an excel sheet on a protected laptop at P336, 3rd floor, UK Department of Psychiatry at 245 Fountain Court (In a locked office and behind a protected firewall). The excel sheets containing the personal information will be saved as an encrypted file every time. A data crosswalk of patient/participant name and MRN will be stored separately from deidentified data and any other research data. Any data sharing will be restricted to the de-identified data. Data will be kept for a minimum of 7 years, and electronically destroyed by UK Policy A13-050 and UK Policy A05-055. For the study proper, urine samples will be collected prior to every TMS session to perform drug screening.
Participant data will be stored in an excel sheet on a protected laptop at P336, 3rd floor, UK Department of Psychiatry at 245 Fountain Court (In a locked office and behind a protected firewall). The excel sheet containing personal information will be saved as an encrypted file every time new data is entered. A data crosswalk of patient/participant name and MRN will be stored separately from the deidentified data. Any data sharing will be restricted to the de-identified data. Data will be kept for a minimum of 7 years, and electronically destroyed by UK Policy A13-050 and UK Policy A05-055. Urine samples will be collected prior to every TMS session to perform drug screening.
Before recruitment of a subject into the study we will phone screen the subject for seizure disorder, as part of recruitment. We will also screen for previous adverse effects to TMS. Prior to the MRI session, we will also screen for metallic implants/devices in the body. This will also be clarified with the subject.

Should a participant voice suicidal ideation at any point during the study, a thorough risk assessment would be completed immediately and the appropriate resources would be contacted including emergency and/or outpatient resources. To mitigate risk of breach of confidentiality or invasion of privacy, all procedures as part of the study will be completed at Fountain Court offices. Participant personal information and medical/psychiatric history will be stored on the University of Kentucky building at Fountain Court. Also, in order to mitigate risk of breach of confidentiality or invasion of privacy, HIPAA will be discussed with each participant at each session.

The main risks with TMS include seizures. We will screen subjects for known risk factors for seizure with rTMS (medical screening and medical history). Personnel who administer rTMS are trained to recognize a potential seizure event and to act as "first responders" to administer appropriate initial care. All study personnel will undergo basic life skills (BLS) training, and seizure-specific training. The major physical signs the study personnel will look out for in detecting a potential seizure include chewing movements, convulsions/tremor/shaking, difficulty talking, a blank stare, eyes rolling up, and profuse sweating. If any of these signs are observed, study personnel will stop the research procedure and inquire whether the subject feels okay. If the subject is unresponsive (and therefore likely experiencing a seizure), first-aid will be supplied. The first-aid response consists of making sure the subject is physically safe for the duration of the seizure. This involves moving the subjects out of the TMS chair and onto the floor lying down on his or her left side. The subject will be kept lying down on his or her left side, while the staff call emergency medical help, via a 911 call. Resources available in the laboratory include a first-aid kit and immediate phone access. A seizure constitutes a reportable adverse event, and will thus be immediately reported to the IRB via the Safety Events Form mechanism.

Initial measures for syncope are identical to those for seizures. TMS will be terminated immediately, and the subject assisted in controlled reclining without impact. Airway breathing and circulation will be assessed. Unless tonic-clonic seizure activity occurs, the subject will be turned on one side to help clear the airway and avoid aspiration.

An MRI procedure is considered to be "minimal risk" according to federal definitions. To date, no after effects have been revealed and the FDA has classified the MR procedure as possessing a "non significant risk" for the subject of study. To minimize risks, all subjects will be screened for metallic devices, implants and other contraindications to scanning. Women of child-bearing capacity will be evaluated for pregnancy using a urine pregnancy test prior to scanning. Those unlikely to tolerate the sense of confinement during scanning will also be excluded. Adequate safety monitoring and observation during scanning will be provided, as will measures to enhance the subject's physical and emotional comfort during the scan. It is possible that some subjects might experience minor distress by the confined and noisy conditions in the scanner. This possibility will be minimized by earplugs and headphones, and experienced technicians who will monitor all subjects for distress. In the event that a subject becomes anxious during a scan, the study will be halted. Subjects will be able to communicate with the investigators at all times using the intercom system should they wish to request that a study be terminated or have concerns or questions during the procedure. The subject is in full view of the operator at all times. The probability of an incidental finding that might lead to the diagnosis of an unknown abnormality is greater than zero. To identify if there any any incidental abnormalities, all scans obtained in this study will be reviewed by the principal investigator Gopalkumar Rakesh who is a board certified psychiatrist. He has experience with reviewing brain MRI scans as part of previous research studies and in his clinical experience. All subjects will be alerted to this possibility during the consent process. In that event, subjects or their designated physician will be provided copies of their anatomical scans and advised to seek further evaluation if they have concerns.Subjects will be transported between 245 Fountain Court and MRISC using UberHealth (www.uberhealth.com) operated and maintained by Department of Psychiatry.

Subjects will be transported between Fountain Court and MRISC using UberHealth. The risk associated with transportation do not exceed any risk associated with vehicle transportation in everyday life.

If subjects experience headaches they can withdraw without any ramifications pertaining to their respective clinic (Bluegrass/SMART/Beyond Birth). If subjects are hurt or get sick because of something that is done in this study, they can immediately call Gopalkumar Rakesh at 857-22-2276. After business hours, they can call the Psychiatry department On Call Group at (859) 226-7063 and explain to the physician that you are a study participant. The physician will determine what type of treatment, if any, is best for you at that time. The medical costs related to care and treatment because of research related harm will be their responsibility. The University of Kentucky Medical Center has no way to provide compensation for research subjects who receive injuries as a result of participating in biomedical and behavioral research. This means that while all investigators will do everything possible in providing careful medical care and safeguards in conducting this research, there is no way in which the institution can pay for the unlikely

occurrence of injury resulting solely from the research itself.

UK IRB policies state that IRB-related research records must be retained for a minimum of 6 years after study closure. Check this item to confirm that you will retain all IRB-related records for a minimum of 6 years after study closure.

Payment

Describe the incentives (monetary or other) being offered to subjects for their participation. If monetary compensation is offered, indicate the amount and describe the terms and schedule of payment. Please review this guidance for more information on payments to subjects, including restrictions and expectations.

Subjects will be compensated monetarily for every session of the study. For participation in the study on day one, they will be paid $50. For days two and three, they will be paid $100 and $200 respectively.

To modify: Subjects will be compensated monetarily for every session of the study. Subjects will receive up to $350 for taking part in this study. They will be paid $50 for day one of the study, $150 for day two of the study and $ 25 for day three, and $25 for day four of the study. If the patient chooses to withdraw from the study after day one or two, they will still receive $50 or $150 respectively and an additional prorated amount depending on the number of hours they spent in the study.

Costs to Subjects

Include a list of services and/or tests that will not be paid for by the sponsor and/or the study (e.g., MRI, HIV). Keep in mind that a subject will not know what is “standard” – and thus not covered by the sponsor/study – unless you tell them.

There will be no cost to the subject to participate in the pilot or main research studies. The University of Kentucky does not have funds set aside to pay for the cost of any care or treatment that might be necessary because subjects get hurt or sick while taking part in this study. Also, the University of Kentucky will not pay for any wages subjects may lose if they are harmed by this study.

Data and Safety Monitoring

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

- If you are conducting greater than minimal risk research, or your clinical investigation is NIH-funded, 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, 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.

Subject data will be de-identified and stored on a spreadsheet on the computer in Fountain Court P336 in a locked office and behind a firewall. The excel sheet containing the personal information will be saved as an encrypted file every time. A data crosswalk of patient/participant name and MRN will be stored separately from deidentified data and any other research data. Prior to administering TMS, all personnel will be trained with the machine. The PI has been trained in TMS from Duke University Medical Center, NC. One of the other co-investigators on the study, Michael Wesley has a TMS suite and will collaborate with the PI to set up safety monitoring and adverse event reporting policies. In addition the PI will work closely with consultants from Duke/NIMH and the research officer with TMS manufacturer Magventure to administer safety monitoring policies for this study. We will institute procedures for promptly detecting harm and mitigating potential injuries. This will also ensure adequate feedback of information to all investigators. Any data sharing will be restricted to the de-identified data. Data will be kept for a minimum of 7 years, and electronically destroyed by UK Policy A13-050 and UK Policy A05-055.
Any adverse events or unanticipated problems would be reported per the IRB’s policy on “Unanticipated Problem and Safety Reporting.” https://www.research.uky.edu/uploads/ori-d20000-irb-policy-unanticipated-problem-and-safety-reporting-pdf

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Future Use and Sharing of Material (e.g., Data/Specimens/Information)

If the material collected for this study will be used by members of the research team or shared with other researchers for future studies, please address the following:

- list the biological specimens and/or information that will be kept
- briefly describe the types, categories and/or purposes of the future research
- describe any risks of the additional use
- describe privacy/confidentiality protections that will be put into place
- describe the period of time specimens/information may be used
- describe procedures for sharing specimens/information with secondary researchers
- describe the process for, and limitations to, withdrawal of specimens/data

WILL YOUR INFORMATION (OR SPECIMEN SAMPLES) BE USED FOR FUTURE RESEARCH?

All identifiable information (e.g., your name, medical record number, or date of birth) will be removed from the information or samples collected in this study. This means that no link or code to your identity will be kept. After all identifiers have been removed, the information or samples may be used for future research or shared with other researchers without your additional informed consent, Once you give your permission to have your de-identified information or samples stored, they will be available indefinitely and cannot be removed due to the inability to identify them.

Are you recruiting or expect to enroll **Non-English Speaking Subjects or Subjects from a Foreign Culture**? (does not include short form use for incidentally encountered non-English subjects)

○ Yes ◉ No

Non-English Speaking Subjects or Subjects from a Foreign Culture

Recruitment and Consent:

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.
When recruiting Non-English-speaking subjects, provide a consent document in the subject's primary language. After saving this section, attach both the English and translated consent documents in the "Informed Consent" section.

Cultural and Language Consultants:

The PI is required to identify someone who is willing to serve as the cultural consultant to the IRB.

- This 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 be involved with the study or have any interest in its IRB approval.
- Please include the name, address, telephone number, and email of the person who agrees to be the cultural consultant for your study.
- ORI staff will facilitate the review process with your consultant. Please do not ask them to review your protocol separately.

For more details, see the IRB Application Instructions on Research Involving Non-English Speaking Subjects or Subjects from a Foreign Culture.

Local Requirements:

If you will conduct research at an international location, identify and describe:

- relevant local regulations
- data privacy regulations
- applicable laws
- ethics review requirements for human subject protection

Please provide links or sources where possible. If the project has been or will be reviewed by a local ethics review board, attach a copy in the "Additional Information/Materials" section. You may also consult the current edition of the International Compilation of Human Research Standards

Does your study involve **HIV/AIDS research and/or screening for other reportable diseases (e.g., Hepatitis C, etc…)**?
◉ Yes ○ No

HIV/AIDS Research

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

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

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

Although the research project involves subjects with a diagnosis of HIV/AIDS, we will not perform HIV testing in these subjects.

PI-Sponsored FDA-Regulated Research

Is this an investigator-initiated study that:

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

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

One of the other co-investigators on the study, Michael Wesley has a TMS suite and will collaborate with the PI to set up safety monitoring and adverse event reporting policies. In addition the PI will work closely with consultants from Duke/NIMH and the research officer with TMS manufacturer Magventure to administer safety monitoring policies for this study. The PI has received TMS training from Duke University, NC. The PI has also taken required CITI courses needed for the role, which are attached herewith.
In accordance with FDA requirements for investigators who are sponsors of non significant risk devices, the PI will label the TMS device with the statement "CAUTION - Investigational Device. Limited by Federal (or United States) law to investigational use." (21 CFR 812.5). The PI will obtain IRB approval before using the device and will maintain IRB approval for the device during its period of use. The PI will also ensure that investigator(s) are complying with FDA, IRB and sponsor requirements. (21 CFR 812.46). The PI will conduct an evaluation of unanticipated adverse events and terminate the study if necessary. (21 CFR 812.46). The PI will resume terminated studies only after receiving approval from the IRB and if terminated due to an unanticipated adverse device effect, also obtain FDA approval to resume the study. (21 CFR 812.46). The PI will ensure that each investigator obtains consent for each subject unless the IRB grants a waiver under 21CFR56.109(c). The PI will also ensure that each investigator maintains accurate and complete records in accordance with FDA regulations and reports the results to the appropriate parties. (21 CFR 812.140 & 21 CFR 812.150). The PI will permit and facilitate monitoring and auditing by the IRB or inspection by federal or state regulatory agencies as appropriate. (21 CFR 812.145). The PI will limit promotion of the device and register the study at ClinicalTrials.gov per the Food and Drug Administration Amendments Act (FDAAA) of 2007 (Public Law 110-85). The PI will also comply with FDA reg

IRB policy requires mandatory training for 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 sponsor-investigator completed the mandatory PI-sponsor training prior to this submission?
◉ Yes ○ No
If the sponsor-investigator has completed equivalent sponsor-investigator training, submit documentation of the content for the IRB's consideration.

Attachments

Attach Type	File Name

SponsorInvTraining	SponsorInvTraining_1.pdf
SponsorInvTraining	SponsorInvTraining_2.pdf
SponsorInvTraining	SponsorInvTraining_3.pdf
SponsorInvTraining	SponsorInvTraining_4.pdf
SponsorInvTraining	SponsorInvTraining_5.pdf
SponsorInvTraining	SponsorInvTraining_6.pdf
SponsorInvTraining	SponsorInvTraining_7.pdf

HIPAA

0 unresolved comment(s)

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.)

I have attached a HIPAA Waiver of Authorization. ○ Yes ◉ No

Attachments

STUDY DRUG INFORMATION

0 unresolved comment(s)

The term drug may include:

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

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

○ Yes ◉ No

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

LIST EACH DRUG INVOLVED IN STUDY IN THE SPACE BELOW

Drug Name:

Note: Inpatient studies are required by Hospital Policy to utilize Investigational Drug Service (IDS) pharmacies (Oncology or Non-Oncology). 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 if the study is being conducted under FDA's Expanded Access Program (e.g., Treatment IND) or if this is an Individual Patient Expanded Access IND (FDA Form 3926).

FDA's Expanded Access Program Information for Individual Patient Expanded Access INDs, and attach the following:

- FDA Form 3926;
- FDA expanded access approval or correspondence;
- Confirmation of agreement from manufacturer or entity authorized to provide access to the product.

For guidance and reporting requirements at the conclusion of treatment see the Expanded Access SOP.

Complete and attach the required Study Drug Form picking "Study Drug Form" for the document type. Any

applicable drug documentation (e.g., Investigator Brochure; approved labeling; publication; FDA correspondence, etc.) should be attached using "Other Drug Documentation" for the document type.

Attachments

STUDY DEVICE INFORMATION

0 unresolved comment(s)

A DEVICE may be a:

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

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

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

◉ Yes ○ No

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

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

LIST EACH DEVICE BEING TESTED IN STUDY IN THE SPACE BELOW

Device Name:

MagProX100 with Magoption Magnetic Stimulator

Is the study being conducted under a valid Investigational Device Exemption (IDE), Humanitarian Device Exemption (HDE) or Compassionate Use?

◉ Yes ○ No

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

The TMS device is FDA-approved for peripheral nerve stimulation (FDA clearance number K051864), and for depression, but not for the specific central nervous system stimulation proposed in this study. The device therefore constitutes an investigational device, for which FDA Investigational Device Exemption (IDE) guidelines apply.
The device complies with FDA labeling requirements (CFR 21 809.10(c), see http://www.accessdata.fda.gov/scripts/cdrh/cfdo FR=809.10), and for the purpose of our proposed investigation, the MagVenture MagProX100 stimulator represents a non- significant risk device because it does not meet the definition of a significant risk device under FDA paragraph 812.3(m) of the investigational device exemptions (IDE) regulation (21 CFR 812) (see http://www.accessdata.fda.gov/scripts/cdrh/cfdo CFRPart=812).

IDE/HDE Submitted/Held by:

Sponsor:	☐	Held By:	
Investigator:	☐	Held By:	
Other:	☑	Held By:	NA

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

For Individual or Small Group Expanded Access, see FDA's Early Expanded Access Program Information, and attach the following:

- FDA expanded access approval or sponsor’s authorization;
- An independent assessment from an uninvolved physician, if available;
- Confirmation of agreement from manufacturer or entity authorized to provide access to the product.

For guidance and reporting requirements at the conclusion of treatment see the Medical Device SOP.

Does the intended use of any research device being tested (not clinically observed) in this study meet the regulatory definition [FDA's PDF] of Significant Risk (SR) device?

- ○ Yes. Device(s) being tested 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 being tested in this study do not present a potential for serious risk to the health, safety, or welfare of subjects/participants.

Complete and attach the required Study Device Form, picking the "Study Device Form" for the document type. Any applicable device documentation (e.g., Manufacturer information; patient information packet; approved labeling; FDA correspondence, etc.) should be attached using "Other Device Documentation" for the document type.

Attachments

Attach Type	File Name
Study Device Form	70889_StudyDevice.pdf

RESEARCH SITES

0 unresolved comment(s)

To complete this section, ensure the responses are accurate then click "SAVE".

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

Research activities conducted at performance sites that are not owned or operated by the University of Kentucky (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), including:

- 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.
- Supportive documentation, including letters of support, can be attached below. When attaching reliance documents, please ensure that you select the correct 'Document Type' from the drop-down menu. See below for the "**Document Types**" in bold, followed by examples of reliance documents for each type:
  - **Individual Investigator Agreement (IIA)**
    - A completed Individual Investigator Agreement

- IRB Approval (Non-UK)
- A Letter of Approval from a Non-UK IRB

- IRB Authorization Agreement (IAA)
- A SMART IRB Agreement
- An OHRP Agreement
- A DoD Agreement
- An IREx Reliance Notification
- Any Reliance Agreement

- Letter of Support & Local Context
- A Letter of Support from an organization at which some research activities are occurring
- Communications Plan
- Local Context Form

Please reach out to IRBReliance@uky.edu if you have any questions or concerns.

- NOTE: 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. For instance, the other site(s) may need to complete their own IRB review, or a cooperative review arrangement may need to be established with non-UK sites.
- Questions about the participation of non-UK sites/personnel should be discussed with the ORI staff at (859) 257-9428.

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

Describe the role of any non-UK site(s) or non-UK personnel who will be participating in your research.

Please describe the plan for the management of reporting unanticipated problems, noncompliance, and submission of protocol modifications and interim results from the non-UK sites:

Attachments

B) If your research involves collaboration with any sites and/or personnel outside the University of Kentucky, then it is considered multisite research and IRB reliance issues will need to be addressed. This may include national multi-center trials as well local studies involving sites/personnel external to UK. If you would like to request that the University of Kentucky IRB (UK IRB) serve as the lead IRB for your study, or if you would like the UK IRB to defer review to another IRB, please contact the IRBReliance@uky.edu.

RESEARCH ATTRIBUTES

0 unresolved comment(s)

Instructions: For various reasons, it is necessary to determine whether your research activities meet the definition of clinical research and/or a clinical trial. Your responses to the next series of questions will make that determination. For more details on the definitions, go to ORI's clinical research vs. clinical trial web page or visit NIH's decision tree for the NIH Clinical Trial definition.

My research activities include one or more of the following:

Patient-oriented research regarding mechanisms of human disease, therapeutic interventions, clinical studies, or development of new technologies
◉ Yes ○ No

Material of human origin (such as tissues, specimens, and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects
○ Yes ◉ No

Epidemiologic or Behavioral Studies
○ Yes ◉ No

Outcomes Research or Health Services Research
○ Yes ◉ No

Does your research study involve one or more human subjects prospectively assigned into one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes?
◉ Yes ○ No

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

☐ Not applicable

Check All That Apply

☐ Academic Degree/Required Research
☐ Alcohol/Drug/Substance Abuse Research
☐ Biological Specimen Bank Creation (for sharing)
☐ Cancer Research
☑ CCTS-Center for Clinical & Translational Science
☐ Certificate of Confidentiality
☐ Collection of Biological Specimens for banking and use
☐ Community-Based Participatory Research
☐ Deception
☐ Educational/Student Records (e.g., GPA, test scores)
☐ Emergency Use (Single Patient)
☐ Gene Transfer
☐ Genetic Research
☐ NIH Genomic Data Sharing (GDS) (databases such as GWAS, dbGaP, GenBank)
☐ Treatment with Human Cells, Tissues, and Cellular and Tissue Based Products
☐ Individual Expanded Access or Compassionate Use

For additional requirements and information:

- Cancer Research (MCC PRMC)
- Certificate of Confidentiality (look up "Confidentiality/Privacy...")
- CCTS (Center for Clinical and Translational Science)
- Clinical Research (look up "What is the definition of....)
- Clinical Trial
- Collection of Biological Specimens for Banking (look up "Banks, Repositories, Registries...")
- Collection of Biological Specimens (look up "Repositories, Registries, Specimen/Tissue Banks...")
- Community-Based Participatory Research (look up "Community-Engaged...")
- Data & Safety Monitoring Board (DSMB)

  *For Medical IRB: Service Request Form for CCTS DSMB

- Data & Safety Monitoring Plan
- Deception*

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

- Emergency Use (Single Patient) [attach

- ☐ International Research
- ☐ Planned Emergency Research Involving Exception from Informed Consent
- ☐ Recombinant DNA
- ☐ Registry or data repository creation
- ☐ Stem Cell Research
- ☐ Suicide Ideation or Behavior Research
- ☐ Survey Research
- ☐ Transplants
- ☐ Use, storage and disposal of radioactive material and radiation producing devices
- ☐ Vaccine Trials

Emergency Use Checklist] (PDF)

- Genetic Research (look up "Banks, Repositories, ...Genetic/Genomic Data Sharing...")
- Gene Transfer

*For gene transfer research, also go to the E-IRB Application Other Review Committees section, and checkmark Institutional Biosafety Committee

- International Research (look up "International & Non-English Speaking")
- NIH Genomic Data Sharing (GDS) Policy (PDF)
- Planned Emergency Research Involving Exception to Informed Consent*

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

- Use, storage and disposal of radioactive material and radiation producing devices

FUNDING/SUPPORT

0 unresolved comment(s)

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

☐ Not applicable

Check All That Apply

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

Click applicable listing(s) for additional requirements and 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-look up "Does the IRB Charge a Fee..."]
- 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

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.):

NA

Add Related Grants

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

Add Related Grants

Grant/Contract Attachments

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

Assurance/Certification Attachments

OTHER REVIEW COMMITTEES

0 unresolved comment(s)

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
- Radioactive Drug Research Committee (RDRC)
- Markey Cancer Center (MCC) Protocol Review and Monitoring Committee (PRMC)** - Attach MCC PRMC materials, if any, per instructions.
- Office of Medical Education (OME)
- Graduate Medical Education Committee (GME)

Attachments

**** If your study involves cancer research, be sure to select "Cancer Research" in the "Research Attributes" section.** ORI will send 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 PRMC review is not required. Your IRB application will be processed and reviewed independently from the PRMC review.

ADDITIONAL INFORMATION/MATERIALS

0 unresolved comment(s)

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

Approval Letter Details:

If you wish to have specific language included in your approval letter (e.g., serial #, internal tracking identifier, etc…), type that language in the box below exactly as it should appear in the letter. The text you enter will automatically appear at the top of all approval letters, identical to how you typed it, until you update it. Don't include instructions or questions to ORI staff as those will appear in your approval letter. **If these details need to be changed for any reason, you are responsible for updating the content of this field.**

Additional Materials:

If you have other materials you would like to include for the IRB's consideration, check all that apply and attach the corresponding documents using the Attachments button below.

- ☐ Detailed protocol
- ☐ Dept. of Health & Human Services (DHHS) approved protocol (such as NIH sponsored Cooperative Group Clinical Trial)
- ☐ Other Documents

Protocol/Other Attachments

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

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

To view the materials currently attached to your application, click “All Attachments” on the left menu bar.

SIGNATURES (ASSURANCES)

0 unresolved comment(s)

Introduction

All IRB applications require additional assurances by a Department Chairperson or equivalent (DA), and when applicable, a Faculty Advisor or equivalent (FA). This signifies the acceptance of certain responsibilities and that the science is meritorious and deserving of conduct in humans. The person assigned as DA *should not* also be listed in the Study Personnel section, and the individual assigned as FA *should* be listed in the Study Personnel section.

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

For a detailed illustration of how to complete this section, please review the short online video tutorial "Signatures (Assurance) Section - How to Complete." Otherwise, follow the steps below.

Required Signatures:

Individuals chosen as signees may remove the application from their Inbox without signing the Assurance Statement by clicking "Return to PI" with a comment about why it is being returned (e.g., specific edits are deemed necessary).

The PI, and personnel chosen as a contact, will receive an email notification that edits are needed, and can find the draft application in both the "Draft" folder and the "Signatures Status" folder located in the menu in the left margin of the default Inbox page. The researcher does not have a 'reply' option to the signee's comments and must make the requested edits directly in the application, or communicate outside the E-IRB system as to why not. Once the response is finalized, the researcher must re-visit the "Assurances Required" section to click the "Return to Signee" button for their re-consideration; the signee will receive an email notification at that time.

Hover your mouse cursor here for additional instructions.

First Name	Last Name	Role	Department	Signee Return Comment	Date Signed	
Seth	Himelhoch	Department Authorization	Psychiatry		07/20/2021 05:23 PM	View/Sign
Gopalkumar	Rakesh	Principal Investigator	Psychiatry		07/21/2021 06:12 AM	View/Sign

Department Authorization

☑ This is to certify that I have reviewed this research protocol and that I attest to the scientific validity and importance of this study; to the qualifications of the investigator(s) to conduct the project and their time available for the project; that facilities, equipment, and personnel are adequate to conduct the research; and that continued guidance will be provided as appropriate. When the principal investigator assumes a sponsor function, the investigator has been notified of the additional regulatory requirements of the sponsor and by signing the principal investigator Assurance Statement, confirms he/she can comply with them.

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

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

Principal Investigator's Assurance Statement

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

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

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

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

*You will be able to "sign" your assurance after you have sent your application for signatures (use Submission section). Once all Assurance Statement signatures have been acquired, return to this section to submit your application to ORI.

SUBMISSION INFORMATION

0 unresolved comment(s)

***** If this Continuation Review entails a change in the scope of your activities to include COVID-19 related research, please insert "COVID19" at the start of your Project and Short Titles.*****

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 cannot be sent to the Office of Research Integrity/IRB.

If applicable, remember to update the Approval Letter Details text box under the Additional Information section

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 you will receive a message 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.

Principal Investigator's Assurance Statement

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

1. Having reviewed all the investigational data from this study, including a compilation of all internal and external unanticipated problems.
2. Having reviewed, if applicable, information from the sponsor including updated investigator brochures and data and safety monitoring board reports.

I also attest that I have reviewed pertinent materials concerning the research and concluded either:

A. The human subject risk/benefit relationship is NOT altered, and that it is not necessary to modify the protocol or the informed consent process,
OR,
B. The human subject risk/benefit relationship has been altered, and have previously submitted or am including with this continuation review submission, a modification of the research protocol and informed consent process.

☑ By checking this box, I am providing assurances for the applicable items listed above.

Your protocol has been submitted.

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	Document Type	File Loaded	Document Description	File Size	Modified By	Mod Date
	ApprovalLetter	ApprovalLetter.pdf		0.092	jchine2	6/13/2025 7:56:04 AM
	AdditionInfoConsiderations	02- John Hankins-Signed Informed Consent-6-16-2022.pdf	02- John Hankins-Signed Informed Consent-6-16-2022	0.419	mel244	6/17/2022 10:19:15 AM
	AdditionInfoConsiderations	01- Signed Informed Consent-Chester Brooks -4-27-2022.pdf	01- Signed Informed Consent-Chester Brooks -4-27-2022	0.435	mel244	6/17/2022 10:19:00 AM
	Advertising	70889-Updated Flyer-June-14-2022-STAMPED.pdf	70889-Updated Flyer-June-14-2022-STAMPED	0.329	mel244	6/17/2022 10:11:03 AM
	ResearchProcedures	(Figure 1) Timeline Tasks for four visits.docx	(Figure 1) Timeline Tasks for four visits	0.012	mel244	3/23/2022 1:59:40 PM
	StudyDesign	(Figure 1) Timeline Tasks for four visits.docx	(Figure 1) Timeline Tasks for four visits	0.012	mel244	3/22/2022 4:41:09 PM
	ResearchProcedures	Bell Email_Clean.docx	Recruitment email_modified clean version	0.015	gra252	9/16/2021 5:40:40 AM
	AdditionInfoConsiderations	Rakesh RL 70889.pdf	Revision Letter - minor revisions	0.207	pkma223	8/19/2021 8:01:27 AM
	StudyPopulation	Phone Script_modified.doc	70889_phone_script	0.027	gra252	7/28/2021 12:21:18 PM
	AdditionInfoConsiderations	CC-OD-21-2050.pdf	Certificate of Confidentiality	0.045	jlkear0	7/21/2021 10:52:56 AM
	StudyDevice	70889_StudyDevice.pdf		2.687	gra252	7/21/2021 6:11:32 AM
	Advertising	70889_business_card PR STAMPED.pdf	Business card	0.081	gra252	7/20/2021 9:33:24 AM
	ResearchProcedures	TMSSideEffects.doc		0.048	gra252	7/18/2021 6:48:14 PM
	ResearchProcedures	TCQ.png		0.089	gra252	7/18/2021 6:47:57 PM
	ResearchProcedures	BIS.pdf		0.016	gra252	7/18/2021 6:47:30 PM
	ResearchProcedures	TAQ.PNG		0.067	gra252	7/18/2021 6:46:22 PM
	SponsorInvTraining	SponsorInvTraining_7.pdf		0.151	gra252	7/18/2021 6:29:11 PM
	SponsorInvTraining	SponsorInvTraining_6.pdf		0.149	gra252	7/18/2021 6:29:01 PM
	SponsorInvTraining	SponsorInvTraining_5.pdf		0.150	gra252	7/18/2021 6:28:50 PM
	SponsorInvTraining	SponsorInvTraining_4.pdf		0.150	gra252	7/18/2021 6:28:40 PM
	SponsorInvTraining	SponsorInvTraining_3.pdf		0.149	gra252	7/18/2021 6:28:30 PM
	SponsorInvTraining	SponsorInvTraining_2.pdf		0.152	gra252	7/18/2021 6:28:19 PM
	SponsorInvTraining	SponsorInvTraining_1.pdf		0.152	gra252	7/18/2021 6:28:03 PM
	StudyDesign	Day3_timeline_tasks.png		0.120	gra252	7/18/2021 6:07:51 PM
	StudyDesign	Day_2_timeline_tasks.png		0.120	gra252	7/18/2021 6:07:43 PM
	StudyDesign	Day_1_timeline_tasks.png		0.092	gra252	7/18/2021 6:07:26 PM

Protocol Changes

Click link to sort Changed Date
Continuation/Final Review RiskLevelChanged changed by gra252 on 6/5/2025 10:53:21 AM
~~N~~Y
Continuation/Final Review RiskLevelChangedDesc changed by gra252 on 6/5/2025 10:53:21 AM
Risk level changed to 1 because the study is closed to enrollment. We are analyzing data acuquired from the study
Expedited Categories XPCategory0 changed by gra252 on 5/29/2025 3:56:01 PM
~~N~~Y
HIPAA HIPAADeIdentificationCertForm changed by gra252 on 5/29/2025 2:33:17 PM
~~N~~
Informed Consent ElectronicConsent changed by gra252 on 5/29/2025 2:32:58 PM
N
Informed Consent InformedConsentParentalPermission changed by jchine2 on 5/29/2025 4:10:15 PM
~~N~~N
Informed Consent StampedConsent changed by jchine2 on 5/29/2025 4:10:15 PM
~~N~~Y
Research Attributes EpidemiologicBehavioralStudies changed by gra252 on 5/29/2025 2:33:49 PM
N
Research Attributes MaterialOfHumanOrigin changed by gra252 on 5/29/2025 2:33:49 PM
N
Research Attributes OutcomesHealthServicesResearch changed by gra252 on 5/29/2025 2:33:49 PM
N
Research Attributes PatientOrientedResearch changed by gra252 on 5/29/2025 2:33:49 PM
Y
Research Sites MultisiteLeadInvestigator changed by gra252 on 5/29/2025 2:33:34 PM
~~N~~
Risk Level RiskCategory changed by gra252 on 5/29/2025 3:56:39 PM
~~2~~1

Study Personnel Changes:

Status	PPIdentity	ProtocolID	PersonID	RoleInProtocol	IsContact	LastName	FirstName	Email	DeptCode	RoomBuilding	SpeedSort	PhoneNum	DeptDesc	AuthorizedConsent	ResponsibilityInProject	Degree	Rank	StatusFlag	IsRemoved	ModBy	ModDate	SFI	IsPIRN	MiddleName
Deleted	1017343	103840	00000124	SP	N	Thornton	Alice	alice.thornton@uky.edu						N	Faculty Advisor	MD		P	Y	jchine2	6/12/2025 9:42:49 AM	N		

Protocol Type Comment by Joanne Hines - ORI to PI on 5/29/2025 4:25:40 PM
Thanks for the phone call Dr. Rakesh - let me know if questions - I'll be back in at 7:30 tomorrow morning - Joanne/257-7467

Protocol Type Comment by Lindsay Schneider - ORI to IRB/PI on 5/29/2025 3:44:07 PM
Based on your answer to Question #1 in the Continuation Review (CR) Form, IRB #70889 now qualifies for Expedited Review. Your CR request has been returned so that you can make the following changes:

1. Revise the RISK LEVEL section to be Level 1: not greater than minimal risk.
2. Revise the PROTOCOL TYPE section to be Expedited.
3. Checkmark the EXPEDITED CATEGORY “originally approved by Full IRB at convened meeting”.
4. Remove the attached consent form(s).
5. Re-submit the revised protocol.

Be sure to complete these tasks with enough leeway for Expedited Review before approval lapse on June 17, 2025.

When you re-submit, your protocol will be managed by one of the Expedited Review staff members at ORI.

Study Personnel Comment by Joanne Hines - ORI to PI on 6/12/2025 9:46:23 AM
Dr. Thornton has not completed training so has been removed as study personnel. Thornton is not PIs "Faculty Advisor" - see attached email correspondence with PI.

Study Personnel Comment by Joanne Hines - ORI to PI on 5/29/2025 4:08:49 PM
Alice Thornton requires Human Subject Protection/HSP refresher training - expired 4/5/25.

Informed Consent Comment by Joanne Hines - ORI to IRB/PI on 5/29/2025 4:11:09 PM
ORI staff updated to check "Stamped Consent Doc(s) Not Needed" because the study is closed to enrollment. Note to IRB/PI/study personnel only

Continuation/Final Review Comment by Joanne Hines - ORI to IRB/PI on 5/29/2025 4:18:15 PM
Question #8 - please change "No" to "Yes" and describe why the risk level has changed (see #1 for reason). The IRB must determine whether the study meets the criteria for expedited review - expedited review requires minimal risk level 1.