

Document Coversheet

Study Title: Adjunctive Transcranial Stimulation to Reduce Impulsivity in Opiate Use Disorder

Institution/Site:	University of Kentucky
Document (Approval/Update) Date:	12/18/2024
NCT Number:	NCT05049460
IRB Number	56570
Coversheet created:	8/12/2025

IMPORTANT NOTE: If you select the wrong IRB type or "Protocol Process Type" while your *Initial Review (IR)* application is in draft, or if your IR application has been returned to you for requested revisions or additional information, you may change your selections. You will not be able to change your selections for "Which IRB" or "Protocol Process Type" after initial *approval* of your application (the option to change your selections is not available for MR or CR).

For guidance, see:

- [Which IRB?](#)
- [Which Protocol Process Type?](#)
- ["Getting Started"](#)

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.

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](#).

Based on your responses to the Continuation Review/Final Review questions, to be in accord with federal policy a final review report must be submitted to properly CLOSE OUT your protocol.

IF YOU WISH TO EXTEND YOUR IRB APPROVAL PERIOD, update your 'Anticipated Ending Date of Research Project' under the Project Information section and include any other supportive documentation for continuation of your study [NOTE: If you wish for your IRB approval to continue, but you do not request an extension and complete and submit your materials in a timely manner, IRB approval will expire at the end of the current approval period.].

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.

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



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.

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

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**.

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.

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:

60

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:

24

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

24

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

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.

Of the 24 participants who were enrolled and signed the informed consent, only two withdrew from the study for personal reasons, including scheduling conflicts and lack of child care.

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.

Participants reported a reduction in cravings for cigarettes and opioids after the iTBS sessions.

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: **3**

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:

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.

10. Project Information

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

12/31/2024

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.

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
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No records to display.

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.

n/a

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.):

n/a

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.

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).

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	1			
Latinx				
Native Hawaiian or Other Pacific Islander				
White	10	13		
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.

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).

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.

56570
CLOSED

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



Adjunctive Transcranial Stimulation to Reduce Impulsivity
in Opiate Use Disorder

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.



Transcranial Stimulation to Reduce
Impulsivity in

Anticipated Ending Date of Research Project: 12/31/2024

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

60

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:	<input type="text" value="Gopalkumar"/>	Room# & Bldg:	<input type="text" value="Fountain Court"/>
Last Name:	<input type="text" value="Rakesh"/>	Speed Sort#:	<input type="text" value="40509"/>
Middle Name:	<input type="text"/>		
Department:	<input type="text" value="Psychiatry - 7H800"/>	Dept Code:	<input type="text" value="7H800"/>
PI's Employee/Student ID#:	<input type="text" value="12461687"/>	Rank:	<input type="text" value="Assistant Professor"/>
PI's Telephone #:	<input type="text" value="8572222276"/>	Degree:	<input type="text" value="MD"/>
PI's e-mail address:	<input type="text" value="gra252@uky.edu"/>	PI's FAX Number:	<input type="text"/>
PI is R.N.	<input type="radio"/> Yes <input checked="" type="radio"/> No	HSP Trained:	<input type="text" value="Yes"/>
		HSP Trained Date:	<input type="text" value="9/15/2022"/>
		RCR Trained:	<input type="text" value="Yes"/>

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

☐ Yes ☒ No

RISK LEVEL

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.

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..) to

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 these resources:

[NIH Diversity Policy](#)

[FDA Diversity Guidance](#)

We will recruit a sample population comprising 60 patients aged 18-60 years with a diagnosis of opiate use disorder from the SMART clinic. If interested in participating and fulfilling inclusion and exclusion criteria, we will provide subjects with information and seek informed consent before proceeding with the study. Inclusion criteria. Potential participants will be: 1) Suboxone maintained patients enrolled in the SMART Clinic; 2) 18-60 years of age; 3) Able to read, understand and communicate in English; 4) Able to attend the SMART Clinic for four consecutive days; 5) willing to adhere to the general rules of the SMART Clinic; 6) willing and able to abstain from drug use other than Suboxone 7) If on Suboxone, should have been on it for at least a week 8) Right handed Exclusion criteria. Traumatic brain injury, h/o seizure disorder, h/o or current diagnosis of schizophrenia, intracranial metal shrapnel, previous adverse effect with TMS, sub-threshold consistency while performing behavioral tasks, lack of attentional bias to opioid cues, positive pregnancy test. Since our study involves MRI brain scans, we will exclude pregnant females in this study. The research project is not connected to the SMART clinic (i.e., a person can be enrolled in the SMART clinic 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.

Attachments

Indicate the targeted/planned enrollment of the following members of minority groups and their subpopulations. Possible demographic sources: [Census Regional Analyst Edition](#), [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:	1			
Black/African American:				
Latinx:				
Native Hawaiian/Pacific Islander:				
White:	7	10		
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

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

ADDITIONAL INFORMATION:

- ☐ 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

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

0 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

Attach Type	File Name
Informed Consent/HIPAA Combined Form	IRB#56570-Consent-TMS-V6-Clean Version.pdf

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, 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 SMART clinic (i.e., a person can be enrolled in the SMART clinic 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.

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

0 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 Getting Started](#) 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	A	C	Contact	Degree	StatusFlag	(HSP)	(HSP)Date	(RCR)	Removed?	Last Updated	SFI	Active
Dicken	Danielle	Data Collection	SP	N	N			P	Y	08/08/2023	Y	N	08/23/2021	N	Y
Garth	Patricia	Study Coordinator	DP	N	N			P	Y	03/13/2023	Y	N	06/05/2023	N	Y
Himelhoch	Seth	Co-Investigator	SP	Y	N			P	Y	07/18/2022	Y	N	07/12/2021	N	Y
Li	Ailing	Co-Investigator	SP	N	N			P	Y	10/19/2023	Y	N	11/15/2023	N	Y
Means	Natalya	Data Collection	DP	Y	Y			P	Y	10/15/2024	Y	N	11/15/2023	N	Y
Mosley	Donavyn	Project Assistance/Support	SP	Y	N			P	Y	05/31/2023	Y	N	06/05/2023	N	N
Rush	Craig	Co-Investigator	DP	Y	N		PhD, Professor	P	Y	08/16/2023	Y	N	04/10/2020	N	Y
Shridas	Preetha	Co-Investigator	SP	N	N			P	Y	10/18/2023	Y	N	11/15/2023	N	Y
Anand	Pavan	Data Collection	SP	Y	N			P	Y	10/18/2022		Y	11/15/2023	N	N
Cordero	Patrick	Data Analysis/Processing	SP	Y	N		MD	P	Y	11/02/2022		Y	12/28/2022	N	N
Czerner-Garcia	Nicole	Project Assistance/Support	SP	Y	N			S	Y	03/03/2022		Y	11/15/2023	N	Y
Elias	Madona	Data Analysis/Processing	DP	Y	Y		MSW	P	Y	07/18/2022	Y	Y	11/15/2023	N	Y
Gawthorp	Noah	Project Assistance/Support	SP	Y	N			P	Y	05/26/2022		Y	12/28/2022	N	N
Gerwe	Christian	Data Collection	SP	N	N			P	N	03/23/2021		Y	11/15/2023	N	N
Jackson	Denisha	Recruitment	SP	N	N			P				Y	08/24/2021	N	Y
Jasinski	Lindsey	Co-Investigator	DP	Y	N		PhD, Assistant Professor	P	Y	08/01/2023	Y	Y	10/19/2022	N	Y
Jenkins	Brooklyn	Project Assistance/Support	SP	Y	N			P	Y	03/29/2022		Y	12/28/2022	N	Y
Khanal	Rebika	Data Collection	SP	Y	N			P	Y	02/04/2022	Y	Y	11/15/2023	N	Y
Khanal	Subash	Data Collection	SP	Y	N			P				Y	07/04/2021	N	N
Kimberlain	Nicholas	Recruitment	SP	N	N			P				Y	02/28/2022	N	Y
Mayer	Whitney	Recruitment	SP	N	N			P	N	05/01/2008	Y	Y	08/24/2021	N	Y
Riley	Elizabeth	Study Coordinator	DP	Y	N			P	Y	06/21/2022	Y	Y	07/04/2021	N	Y
Su	Amanda	Data Analysis/Processing	SP	Y	N		MD	P	N	06/02/2021		Y	11/15/2023	N	N
Thomas	Mareena	Project Assistance/Support	SP	Y	N			P	Y	04/28/2022		Y	12/28/2022	N	N
Tindell	William	Data Collection	SP	N	N			P	N	06/26/2021		Y	11/15/2023	N	N
PhD,															

56570
CLOSED

Last Name	First Name	Responsibility In Project	Role	A C	Contact	Degree	StatusFlag	(HSP)	(HSP)Date	(RCR)	Removed?	Updated
Wesley	Michael	Co-Investigator	DP	Y	N	Assistant Professor	P	Y	11/07/2023	Y	Y	11/15/2023 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).

1.1. Epidemiology

Opiate use disorder (OUD), including heroin, prescription opioids and fentanyl, contributes to approximately 130 overdose deaths per day in the US (1, 2). Healthcare costs from the opioid crisis ranged approximately \$1 trillion in 2017 and is expected to increase in the future(3). Standard-of-care relapse prevention strategies for OUD include pharmacological options like buprenorphine, methadone and naltrexone (4). However, the efficacy of these interventions are suboptimal in that relapse rates remain stubbornly high (i.e., 50-60%) (5). These findings along with the overdose death data described above underscore the urgent need to identify and implement innovative interventions for OUD to augment the efficacy of medications to promote continued abstinence from illicit opioid use.

1.2 Impulsivity and Attentional Bias in Opioid Use Disorder (OUD)

Theoreticians have proposed that drug-use decisions are governed by the interaction of two systems: Impulsive and Executive (6-8). The Impulsive System is fast and associated with automatically triggered or reflexive approach responses. The Executive System, by contrast, is slower and associated with deliberation, self-regulation and restraint. According to the Dual-Processing Theory, substance use disorders (SUDs) in general and opioid use disorder in particular are, in part, attributable to an imbalance between these distinct neurobiological systems with the Impulsive System dominating ((9-14)

Impulsivity is a multi-faceted construct and closely tied with neurobiology of substance use disorders (15, 16). Although it is plausible that impulsivity is a result of substance use, an alternative hypothesis pitches it as a vulnerability marker leading to development of or worsening of substance use disorder (15-17). This makes it attractive as an intervention point to ameliorate neurotoxic and other physiological outcomes of chronic substance use (16-18).

Laboratory tasks have been developed to study different facets (15, 19). One facet of impulsivity is difficulty suppressing pre-potent responses, sometimes referred to as motor impulsivity (17, 20, 21) measured using Stop-Signal and Go/No-Go tasks (22-26). Another facet of impulsivity is difficulty delaying gratification, defined as a preference for smaller, immediate rewards over larger, delayed rewards, and measured using hypothetical discounting tasks (27-29). Consistent with the Dual-Processing Theory, chronic opioid use results in impulsive responding on Stop-Signal, Go/No-Go tasks (16, 30) and delay discounting tasks (30-32).

Another cognitive facet that could assist as a biomarker to assess interventions for impulsivity in OUD is attentional bias (33).

Attentional bias refers to the tendency to attend to, and maintain attention on, drug-related cues, rather than neutral cues (25, 34, 35). Measured with eye tracking using a visual probe, this bias has been demonstrated in patients with opiate use disorder (OUD), even while on opiate replacement therapy (35). Measuring attention bias with eye tracking would provide a physiological biomarker to measure the impact of any intervention designed to reduce impulsive decision making in OUD (12, 36).

1.3 Transcranial Stimulation to Reduce Impulsivity, Attention Bias and serve as an adjunctive treatment to suboxone for OUD

Non-invasive brain stimulation (NIBS) is a novel intervention that uses modulated doses of electric current to change neural activity. In psychiatric illnesses like major depressive disorder (MDD) and schizophrenia, NIBS including electroconvulsive therapy (ECT) and transcranial magnetic stimulation (TMS) have been used to augment medication treatments or treat residual symptoms, which are addressed sub-optimally by pharmacotherapy (37, 38). TMS uses a magnetic field to generate electric current at a focal brain site, leading to modulation in neural activity and consequently symptoms and behavior (39).

TMS has also been used to modulate cognitive performance in healthy controls (40) and SUDs (41, 42). The stimulation changes neural activity, as seen in studies that utilize concurrent TMS and neuroimaging. Three previous studies have used TMS to modulate delay discounting (41). Two studies delivered 10 Hz rTMS and continuous theta burst stimulation to the medial prefrontal cortex and right DLPFC respectively in healthy controls, causing a shift to delayed rewards over immediate rewards (43, 44). One study applied 10 Hz and 20 Hz to left DLPFC in cigarette smokers to cause the same change in delay discounting (45). TMS has been shown to influence selective attention in healthy controls (46, 47). We did not come across any studies where NIBS has been used to modulate attention bias in opiate use disorder, one study used high frequency TMS to modulate attention related to emotional stimuli in subjects with methamphetamine use disorder (48).

1.4 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 have been only three studies that used TMS in OUD. None of them used theta burst stimulation or examined attentional bias to opioids as an outcome measure.

1.5 Stress induced craving paradigm. The pathophysiology of substance use includes the interaction between stress and body physiology, fuelling the illness(63). Multiple previous studies have modeled craving in the presence of stress, to approximate real world scenarios(64-66). We will explore whether 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 opioid craving questionnaire and tobacco craving questionnaire (TCQ).

1.6 Brain network connectivity 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 changes in the salience network to be germane to opioid use disorder. We will explore whether TBS causes changes in resting state functional connectivity in patients with OUD.

Interventions targeting impulse decision making and attentional bias may augment pharmacotherapy, reduce illicit opioid use and improve clinical outcomes such as relapse and frequency of use. While aiming to design an adjunct TMS intervention to augment relapse prevention with suboxone, we aim to use it to impact attentional bias, as well as craving for cigarettes and opioids in OUD. fMRI studies have shown the left dorsolateral prefrontal cortex (DLPFC) to be a nodal area for selective attention and craving.

People 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 people who smoke than people who do not smoke.

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These are changes we request in this modification request :-

1. Instead of four consecutive sessions of 20 Hz TMS versus sham TMS, subjects will now receive four sessions of theta burst stimulation (TBS) (50 Hz, 1800 pulses in each session) on a single day. Each of these sessions will last ten minutes and be separated by 50 minutes from the next session. Every subject will receive both TBS and sham TMS, on separate days in a randomized manner with counter balancing.

2. We will perform a phone screen on subjects interested in the study to determine eligibility and recruit them. We will not review patient charts to determine eligibility.

3. In addition to clinical outcomes like craving, cognitive outcome measures and attentional bias we will now perform a stress induction procedure along with assessment of craving. This has been published about before and is talked about in detail in the research procedure section.

4. To help with TMS targeting, we will obtain functional MRI of brain at baseline and after every set of sessions (TBS and sham TMS) at MRISC located near Markey Cancer Center.

Objectives

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

To demonstrate whether TBS improves attentional bias and craving in OUD compared to sham stimulation. We hypothesize 4 sessions of TBS to the left DLPFC will significantly improve attentional bias and craving for smoking and opioid cues compared to

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 randomized controlled trial. Recruitment for the study will be done by research assistant and/or principal investigator. All subjects will receive either TBS or sham stimulation in a randomized manner. 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.

In this study subjects may be randomized into active TMS stimulation or placebo stimulation. In the active TMS stimulation arm, they will receive four sessions of theta burst stimulation (TBS). In the placebo stimulation arm, they will receive four sessions of sham TMS using the MagVenture active/placebo coil that delivers sham TMS. This coil mimics the sound of active TMS and also delivers a superficial electrical stimulation that mimics active TMS. 30 subjects will be randomized to receive active TMS and 30 subjects will be randomized to receive sham TMS. This is done so that there are no carryover residual effects from one arm to the other. In an ongoing TMS study, we have seen carryover residual effects when the same subject got both active and sham TMS in separate sessions.

A sequential timeline of assessments and interventions is shown in Figure 1. On day one of the study, we will perform baseline assessments including breath alcohol level, opioid and tobacco craving questionnaires, opioid and 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 using UberHealth for collection of their baseline MRI brain scan that will last thirty minutes. 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 day, 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). Along with the stimulation, subjects will also perform a host of other tasks as shown in figures 2 and 3. The figures also indicate the timing of these tasks. Craving for opioids and 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 in background). 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.

Tasks on Day 1 attached as figure 1 in attachments

Tasks accompanying active TBS stimulation on day 2 attached as TBS_Day2 in attachments

Tasks accompanying sham TMS stimulation on day 2 attached as Sham TMS_Day2 in attachments

All devices apart from the TMS device (MagPro R100) are not study devices.

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.

Attachments

Attach Type	File Name
StudyDesign	TBS_Day2.png
StudyDesign	Sham TMS_Day2.png
StudyDesign	Figure 1.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 Fountain Court clinic. Study members will interface with all providers in the clinic on a daily basis. All providers in the clinic will be provided multiple copies of the study brochure. All providers in the clinic will also be informed about inclusion and exclusion criteria for the study, based on which all patients will be screened by them. A study member will consistently be present in the clinic everyday. All providers in these clinics will be provided multiple copies of the study flyer. 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. The PI (Dr Rakesh) and a research assistant will interface with a contact in each of these clinics on a daily basis. The study research coordinator will email the study flyer to patients via email as well. 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 PI (Dr Rakesh). He or the research assistant will administer a phone script to subjects who call back to assess subjects' suitability for the study. Initial contact will be made with potential subjects by those having legitimate access to the subjects' identity and the subjects' information. No medical records will be accessed at any point (before, during or after the study). A UK medical record will not be created for the subject. Subjects will be provided information about the study via a study flyer that lists contact numbers for the PI (Gopalkumar Rakesh).

Attachments

Attach Type	File Name
Advertising	Updated- 56570_flyer-Dec-06-2022- Clean Version -PDF.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, we will perform baseline assessments including breath alcohol level, opioid and tobacco craving questionnaires, opioid and 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. The MRISC is situated in the basement of 740 Rose St. 40 Whitney Hendrickson Bldg, Lexington, KY 40536-0098. 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 versus day three 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 2 and 3. Craving for opioids and 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 in background) 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.

Motor Threshold Determination on day one:

Motor threshold (MT) is defined as the TMS pulse amplitude needed to elicit an EMG response of 50 μ V 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 μ V 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.

TMS application on days two and three

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. 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 120 % of resting motor threshold as reported in a previous studies. The participant will be seated comfortably with headphones and earplugs to protect the subject's hearing. We will collect heart rate data using a Fitbit that participants will strap on their wrists on the day of the study.

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. We will explore whether 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 opioid craving questionnaire and tobacco craving questionnaire (TCQ).

Attentional Bias task

We will have subjects perform two types of attentional bias tasks. One type will involve smoking and neutral cues. The other type will involve opioid and neutral cues. Subjects will perform four versions of each task. For smoking 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). For opioid task, we will measure Smoking and neutral cues will be presented side-by-side on the screen for 1000?milliseconds. For opioid task, we will measure attentional bias using a validated database of opioid and neutral cues and Tobii Pro Fusion 120 Hz eye tracker (Tobii Technology, Sweden). 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.

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.

Delay 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 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.

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.

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

Opioid craving questionnaire - The Opioid Craving Scale is a modification of the Cocaine Craving Scale. It consists of three items rated on a visual analogue scale from 0–10.

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/>

Attachments

Attach Type	File Name
ResearchProcedures	CC-OD-21-2096.pdf
ResearchProcedures	70637_ResearchProcedures_520334.doc
ResearchProcedures	56570_phone_screen_clean.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
Delay discounting task
Attention bias behavioral activation (ABBA) task using go/no go
Barratt impulsiveness scale (BIS-11)
Tobacco Craving questionnaire (TCQ)
Opioid craving questionnaire
TMS Side effects scale
Treatment acceptability questionnaire (TAQ)
Resting state functional magnetic resonance imaging (fMRI)
Heart rate data from Fitbit

Neuroimaging data will be acquired on a Siemens 3-Tesla (3T) PRISMA scanner at the Magnetic Resonance Imaging and Spectroscopy Center (MRISC), situated close to Markey Cancer Center. 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)

Attachments

Attach Type	File Name
DataCollection	TCQ-SF.png
DataCollection	TAQ.PNG
DataCollection	Opiate craving scale.PNG
DataCollection	BIS11English.pdf
DataCollection	Neutral Images.pdf
DataCollection	Opioid Images.pdf
DataCollection	Scale_side effects.doc

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 with 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. It is part of the David Mills entity. 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, ETCO2, 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. 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.'

The 3T PRISMA MRI machine used as part of the study does not meet the criteria for a study device.
(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?)

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. 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

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 (15), 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). The levels of stimulation used in this protocol are well within safety guidelines (Rossi et al., 2009; Wassermann et al. 1998).

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.

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 TMS/CG. 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.
Wassermann EM. Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5-7, 1996. Electroencephalogr Clin Neurophysiol. 1998;108(1):1-16.

The 3T PRISMA MRI machine used as part of the study does not meet the criteria for a study device.

(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?)

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 this 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 the SMART 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 with opiate use disorder.

Rossi S, Hallett M, Rossini PM, Pascual-Leone A, Safety of TMS. 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).

Since this is not a treatment study, no alternative treatments will be offered.

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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). 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.

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). 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 Urine samples will be collected for drug screens on days two and three of the study.

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.

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. 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 the SMART clinic. If you believe you are hurt or get sick because of something that is done in this study, you should immediately call Gopalkumar Rakesh at 857-22-2276. After business hours, please 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 your care and treatment because of research related harm will be your 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 day two they will be paid \$150.

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 for subjects to participate in 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. 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.

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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.

AUTHORIZATION TO USE OR DISCLOSE YOUR IDENTIFIABLE HEALTH INFORMATION

The privacy law, HIPAA (Health Insurance Portability and Accountability Act), requires researchers to protect your health information. The following sections of the form describe how researchers may use your health information.

The Researchers may use and share your health information with:

- The University of Kentucky's Institutional Review Board/Office of Research Integrity;
- Law enforcement agencies when required by law;
- University of Kentucky representatives;
- UK Hospital
- Food and Drug Administration

The researchers agree to only share your health information with the people listed in this document. Should your health information be released to anyone that is not regulated by the privacy law, your health information may be shared with others without your permission; however, the use of your health information may still be regulated by applicable federal and state laws.

You may not be allowed to participate in the research study if you do not sign this form. If you decide not to sign this form, it will not affect your:

- Current or future healthcare at the University of Kentucky;
- Current or future payments to the University of Kentucky;
- Ability to enroll in any health plans (if applicable); or
- Eligibility for benefits (if applicable).

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)

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**☐ Yes ☒ No**HIV/AIDS Research**

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

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

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

PI-Sponsored FDA-Regulated Research

Is this an investigator-initiated study that:

- 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 regulations on electronic records and electronic signatures and FDA financial disclosure requirements (21 CFR 54).

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](#)

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 ☒ NoIf 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 c
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/cfdocs/cfcfr/CFRSearch.cfm?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/cfdocs/cfcfr/CFRSearch.cfm?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.

Does the intended use of any research device being tested (not clinically observed) in this study meet the regulatory [definition](#) 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	MagVentureX100.pdf
Study Device Form	IRB_IDE_device.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.
- 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 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 involve one or more human subjects prospectively assigned into one or more health-related biomedical or behavioral 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
- ☐ International Research
- ☐ Planned Emergency Research Involving Exception from

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

*For Medical IRB: [Service Request Form](#) for CCTS DSMB

- [Data & Safety Monitoring Plan](#)
- [Deception*](#)

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

- [Emergency Use \(Single Patient\) \[attach Emergency Use Checklist\]](#) (PDF)
- [Genetic Research](#) (look up "Specimen/Tissue

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

Collection...")

- [Gene Transfer](#)
- [HIV/AIDS Research](#) (look up "Reportable Diseases/Conditions")
- [Screening for Reportable Diseases \[E2.0000\]](#) (PDF)
- [International Research](#) (look up "International & Non-English Speaking")
- [NIH Genomic Data Sharing \(GDS\) Policy](#) (PDF)
- [Planned Emergency Research Involving Waiver of Informed Consent*](#)

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

- [Use, 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) [\[IRB Fee Info\]](#)
- [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.):

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 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 and attach form
- [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

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 Needed" 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	
Gopalkumar	Rakesh	Principal Investigator	Psychiatry		03/09/2020 09:29 AM	View/Sign
Elizabeth	Arnold	Department Authorization	Psychiatry		12/13/2023 08:55 AM	View/Sign

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). Please notify the personnel required for signing your IRB application after sending for signatures. Once all signatures have been recorded, you will need to return to this section to submit your application to ORI.

Department Authorization

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

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:

- The human subject risk/benefit relationship is unaffected, mitigated, or eliminated by closure of the study and all pertinent materials for closure of the research are being submitted to the IRB for consideration.

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

Your protocol has been submitted.

Download all

	Document Type	File Loaded	Document Description	File Size	Modified By	Mod Date
🔗	StudyClosure	StudyClosure.pdf		0.079	jlkear0	12/18/2024 11:21:00 AM
🔗	Informed ConsentHIPAA Combined Form	IRB#56570-Consent-TMS-V6-Clean Version.pdf	ICF Clean	0.205	gra252	1/16/2024 6:57:31 AM
🔗	AdditionInfoConsiderations	Protocol Violation_corrective_action.docx	CAPA related to CR submission	0.014	pkma223	12/21/2023 11:29:52 AM
🔗	Advertising	Updated- 56570_flyer-Dec-06-2022-Clean Version -PDF.pdf	Updated- 56570_flyer-Dec-06-2022-Clean Version -PDF	0.325	mel244	12/6/2022 9:25:15 AM
🔗	StudyDesign	Sham TMS_Day2.png	Study design_schedule_Sham_TMS_Day2	0.102	gra252	8/23/2021 2:13:41 PM
🔗	StudyDesign	TBS_Day2.png	Study design_schedule_TBS on Day2	0.112	gra252	8/23/2021 2:12:58 PM
🔗	ResearchProcedures	56570_phone_screen_clean.doc		0.027	gra252	8/5/2021 12:15:02 PM
🔗	ResearchProcedures	70637_ResearchProcedures_520334.doc		0.031	gra252	8/5/2021 12:13:48 PM
🔗	ResearchProcedures	CC-OD-21-2096.pdf	Approved certificate of confidentiality	0.043	gra252	8/3/2021 3:45:28 PM
🔗	AdditionInfoConsiderations	Rakesh Revision Letter MR 56570.pdf	Revision Letter	0.195	pkma223	7/29/2021 2:47:08 PM
🔗	DataCollection	TCQ-SF.png	TCQ	0.089	gra252	7/12/2021 6:20:56 AM
🔗	StudyDesign	Figure 1.png	Tasks on Day One	0.096	gra252	7/7/2021 12:48:00 PM
🔗	StudyDevice	IRB_IDE_device.pdf	IDE_Device_Descriptions	2.676	gra252	6/17/2020 10:35:34 AM
🔗	DataCollection	Opiate craving scale.PNG		0.023	gra252	6/17/2020 10:25:05 AM
🔗	DataCollection	TAQ.PNG		0.067	gra252	6/17/2020 10:24:54 AM
🔗	StudyDevice	MagVentureX100.pdf		0.262	gra252	3/12/2020 6:38:02 AM
🔗	DataCollection	Scale_side effects.doc		0.048	gra252	3/9/2020 8:58:58 AM
🔗	DataCollection	Opioid Images.pdf		12.902	gra252	3/8/2020 5:51:19 PM
🔗	DataCollection	Neutral Images.pdf		11.713	gra252	3/8/2020 5:50:56 PM
🔗	DataCollection	BIS11English.pdf		0.016	gra252	1/20/2020 12:00:08 PM

Protocol Changes

Protocol Number 56570

56570
CLOSED

Click link to sort [Changed Date](#)

HIPAA HIPAA Deidentification Cert Form changed by paga222 on 12/13/2024 11:40:32 AM

N

Informed Consent Electronic Consent changed by paga222 on 12/13/2024 11:35:58 AM

N

Research Attributes Epidemiologic Behavioral Studies changed by gra252 on 12/16/2024 10:51:23 AM

N

Research Attributes Material Of Human Origin changed by gra252 on 12/16/2024 10:51:23 AM

N

Research Attributes Outcomes Health Services Research changed by gra252 on 12/16/2024 10:51:23 AM

N

Research Attributes Patient Oriented Research changed by gra252 on 12/16/2024 10:51:23 AM

Y

Research Sites Multisite Lead Investigator changed by paga222 on 12/13/2024 11:40:49 AM

N

Study Personnel Changes:

No comments



Consent to Participate in a Research Study

KEY INFORMATION FOR Adjunctive Transcranial Magnetic Stimulation (TMS) To Modulate Impulsivity in Opiate Use Disorder (OUD)

We are asking you to choose whether or not to volunteer for a research study about the effects of non-invasive, non-significant risk transcranial magnetic stimulation on how your brain makes decisions and focuses attention. We are asking you because you fulfill eligibility criteria for the study. You are also being asked to participate because you have expressed interest in participating in this study, and because you passed the medical screen. If you volunteer to take part in this study, you will be one of about 60 people to do so at the University of Kentucky. This page is to give you key information to help you decide whether to participate. We have included detailed information after this page. Ask the research team questions. If you have questions later, the contact information for the research investigator in charge of the study is below.

WHAT IS THE STUDY ABOUT AND HOW LONG WILL IT LAST?

The purpose of this study is to learn more about how non-invasive, non-significant risk transcranial magnetic stimulation influences the brain's decision-making process and visual attention. By doing this study, we hope to learn how the brain chooses short term versus long term rewards, in addition to learning how your eyes focus attention when seeing images related to opiates versus neutral images. Your participation in this research will last about four days. This is a research project, not a treatment program. The transcranial stimulation we use is called transcranial magnetic stimulation (TMS). In this study, TMS will be used in a manner which is an investigational procedure, aimed at temporarily changing the way that a part of your brain works. TMS has been approved by the Food and Drug Administration (FDA) as a treatment for depression, but in this study TMS is being used to investigate if changes in the activities of certain areas of the brain affect memory so is therefore considered "investigational". The word "investigational" means TMS is still being tested in research studies and is not approved by the FDA for opiate use disorder.

WHAT ARE KEY REASONS YOU MIGHT CHOOSE TO VOLUNTEER FOR THIS STUDY?

This research study may have direct benefit to you for smoking cessation. The study will inform us about how transcranial magnetic stimulation affects cognitive functions in tobacco use. For a complete description of benefits, refer to the Detailed Consent.

WHAT ARE KEY REASONS YOU MIGHT CHOOSE NOT TO VOLUNTEER FOR THIS STUDY?

This study requires you to come to 245 Fountain Court for two days and to Magnetic Resonance Imaging and Spectroscopy Center (MRISC) for 2 days. If this will be an issue, you may not want to volunteer for this study. For a complete description of risks from the study, refer to the Detailed Consent and/or Appendix. If you experience headaches from the TMS procedure, you can withdraw from the study without ramifications regarding your clinical care.

DO YOU HAVE TO TAKE PART IN THE STUDY?

If you decide to take part in the study, it should be because you really want to volunteer. You will not lose any services, benefits or rights you would normally have if you choose not to volunteer.

WHAT IF YOU HAVE QUESTIONS, SUGGESTIONS OR CONCERNS?

If you have questions, suggestions, or concerns regarding this study or you want to withdraw from the study contact Gopalkumar Rakesh MD, Assistant Professor, Department of Psychiatry at 859-382-7611 during regular business hours. If outside regular business hours, please contact the Psychiatry department On Call Group at (859) 226-7063 and explain to the physician that you are a study participant.

If you have any concerns or questions about your rights as a volunteer in this research, contact staff in the University of Kentucky (UK) Office of Research Integrity (ORI) between the business hours of 8am and 5pm EST, Monday-Friday at 859-257-9428 or toll free at 1-866-400-9428.

DETAILED CONSENT:

ARE THERE REASONS WHY YOU WOULD NOT QUALIFY FOR THIS STUDY?

You should not participate if you have a history of epilepsy or seizures, current or past history of schizophrenia, metal implants or shrapnel in your head, or history of previous adverse events with TMS. If you are a female, you should not participate if you are pregnant or plan on becoming pregnant during your participation in this experiment. You must be using an effective form of birth control (e.g. birth control pills, surgically sterilized, IUD, cervical cap with a spermicide, or abstinence), and you must be willing to take a pregnancy test before being accepted into the research study.

WHERE WILL THE STUDY TAKE PLACE AND WHAT IS THE TOTAL AMOUNT OF TIME INVOLVED?

The research procedures will be conducted at the TMS Research Suite, Department of Psychiatry, 245 Fountain Court, Lexington, Kentucky 40509, right after your SMART clinic appointment. You will need to come in two times during the study. Each of these visits will take about 3-5 hours. The total amount of time you will be asked to volunteer for this study is 10-12 hours over the two main days. The research team will follow up with you at one-week and two-week intervals with a urine cotinine test after completing your two TMS sessions. The two follow-up short visits will last for 2-3 minutes only and will be performed in the SMART clinic lab space.

WHAT WILL YOU BE ASKED TO DO?

If you agree to take part in this study, in your first visit, you will be asked to sign and date this consent form prior to any procedures. You will then be asked to provide a sample for urine drug screen and undergo an alcohol breathalyzer test. You will also undergo psychiatric screening, including questionnaires to rule out major psychiatric illnesses. We will also administer scales to assess craving for cigarettes and impulsive behavior. You will also perform cognitive tasks to measure your visual attention bias towards cigarettes. If you are a woman of childbearing potential, you will also undergo a urine test to make sure you are not pregnant. Then we will ask you to get a brain MRI scan on day one. MRI uses magnetic fields to measure brain structure and brain activity. It involves lying down on a padded platform that is loaded into the circular center of the MRI machine. During a scanning session, you will be asked to remain still as images of your brain are acquired. You will be instructed to remove all jewelry and other metal-containing objects. Because the magnetic field will affect any metallic object, you should not participate if you have any type of metallic implant in your body, including pacemakers, aneurysm clips, shrapnel, metal fragments, orthopedic pins, screws, or plates, IUD's, or piercings that you cannot remove.

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. We will also measure your resting heart rate on day two using EKG leads. This will be done 4 times on day 2, and each instance will last 10-15 minutes. We will also collect 2 ml of your blood on days 1 and 2 of the study to measure an inflammatory marker called high sensitivity C-Reactive Protein (hs-CRP).

Study Task	Study Day 1	Study Day 2	Study Day 3	Study Day 4
Attentional Bias for opioids	X	X		
Attentional Bias for cigarettes	X	X		
MRI brain scan at MRISC	X	X		
Motor threshold	X			
Theta Burst Stimulation (TBS) or sham TMS		X		
Sham TMS		X		
Delay Discounting task	X			
Barrett Impulsiveness Scale	X	X		
Stress Induction Procedure		X		
Behavioral Scales to measure impulsivity and depressive symptoms	X	X		
ACCUTEST Urine cotinine tests	X	X		
Resting EKG to measure heart rate variability		X		
Blood draws for CRP	X	X		

The TMS equipment consists of an electric stimulator and a wire coil. Turning the stimulator on and off produces brief electrical currents in the coil, and these currents create a short-lived magnetic field around that coil (also called a 'magnetic pulse'). The wire coil is coated in plastic in order to insulate the stimulator current, it is shaped like an '8', and it is a little larger than a letter-size piece of paper. When the coil is held close to the head, and it generates a magnetic pulse, the pulse can induce very small electric currents in the part of the brain that is closest to the coil. These currents are similar to the currents that the neurons in the brain produce when communicating with each other. By inducing these currents with the TMS coil, we can temporarily change the way that brain region functions, either making the region work harder or less hard. In this study, TMS will be used in a manner which is an investigational procedure, aimed at temporarily changing the way that a part of your brain works. TMS has been approved by the Food and Drug Administration (FDA) as a treatment for depression but in this study TMS is being used to investigate if changes in the activities of certain areas of the brain affect memory. Although the form of TMS we use has not been approved by FDA for smoking cessation, another type of TMS called deep TMS has been approved by the FDA.

Before applying TMS, the study doctors will need to determine what strength of stimulation to use for you by establishing your personal "motor threshold" – a measure of the excitability of the area of the human brain called the motor cortex. To establish this threshold, the study doctor or a member of the study staff will first place the stimulator over the part of your brain that controls the motor activity in your right hand. You will hear a clicking sound and feel a tapping sensation at your scalp. The stimulator will be adjusted to give just enough energy so that the motor region of the brain sends signals to your hand muscles, to make your hand twitch. The smallest amount of energy required to make your hand twitch is called the "motor threshold." Everyone has a different motor threshold. This procedure will take about 20 minutes and will be done only on day one of the study. Then we will administer cognitive tests to assess how your brain makes decisions and chooses hypothetical rewards. You will also perform a visual attention test to assess how your eyes focus attention when seeing images related to smoking versus neutral images. You will then receive actual TMS versus placebo TMS depending on the group you were assigned to by chance initially. Both groups will get stimulation for 10 minutes.

Regardless of your group assignment, you will be seated comfortably in a chair, facing a computer screen placed about 5 feet away. Earplugs will be worn to protect your hearing. Your head will be held steady by a frame with a chin rest and the TMS coil holder frame, and study staff will ensure your comfort during the entire procedure. The study staff will administer the magnetic stimulation. You will be required to sit still while you receive the stimulation. To block out the clicking noise of the TMS procedure, we will provide you with earplugs. After each TMS session, you will then be administered the cognitive tests, craving and impulsivity scales again. The motor threshold will take

place only on day one. On day one and all other days, you will perform the urine drug screens, alcohol breathalyzer test, receive the stimulation and perform cognitive tests, the visual test and scales before and after stimulation.

The research team will follow up with you at one-week and two-week intervals with a urine cotinine test after completing your regular weekly visit to the SMART clinic. The ACCUTEST urine cotinine tests from Janet Pharmacocal and carbon monoxide testing using Smokerlyzer. These will be performed in the SMART clinic lab space. The ACUTEST cotinine urine test is a qualitative test and indicates the presence or absence of cotinine in your body. Cotinine is a metabolite of nicotine, and these measures will help assess abstinence from cigarette smoking in response to your TMS intervention.

WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS?

Because of your participation in this study, you are at risk for the following side effects. You should discuss these with the researchers and your regular health care provider. The most serious known risk of TMS is the production of a convulsion (seizure). TMS procedures are associated with a very low risk of seizures. Out of tens of thousands of people given various forms of TMS to date, 16 people have been reported to have had a seizure. TMS can produce a convulsion when a series of pulses is given at high power and when repeated series of pulses are given extremely close together. This study will use only levels of TMS that are within safety guidelines. Levels of TMS that fall within the safety guidelines have not been associated with seizure in appropriately screened individuals. No seizures have occurred in normal volunteers with the dosage of TMS used in this study. To minimize this risk, we will medically screen you for any of the known characteristics that could lead to seizure. For example, if you have epilepsy you cannot participate in this study. You will be visually monitored during the TMS for any signs of seizure or muscle twitching. In spite of these precautions, there is a chance that you will experience a convulsion. Should this occur, our study doctor will be called and will assess if you need to be taken to the Emergency Department at UK Medical Center.

If you have a convulsion, you may require hospital admission and follow-up neurological evaluation. Having had a convulsion may make it difficult for you to obtain medical insurance, future employment, and to drive. It is not known whether having had one convulsion will make a person more prone to have future convulsions. Should you have a seizure caused by TMS in this protocol, we will provide you with a letter documenting that the seizure was experimentally induced.

The most common side effect of TMS is a "muscle-tension" type headache. We expect that about three out of ten people may experience a headache with the types of TMS used in this study. We will make every effort to reduce any discomfort by adjusting the position of the TMS coil on your head, altering the stimulation output of the coil, or taking breaks as required. If a headache occurs, it usually starts during or immediately after the TMS and lasts from minutes to hours after TMS. The headache usually goes away with standard over-the-counter pain medications. Neck pain may also occur. You may also experience some discomfort on your head where the coil is held. This is due to contraction of scalp muscles. Temporary numbness of the face has also been reported in rare instances that may last for several weeks after treatment. Fainting (syncope) is also a common reaction to anxiety and psycho-physical discomfort. If this occurs we will have you lie down for a few minutes and have you get up only when you have recovered.

The click noises produced by the TMS procedure are loud enough to be damaging to your ears. You will therefore be required to wear earplugs, provided by the experimenter. Additional side effects considered to be rare in TMS are dizziness, memory impairment, trouble concentrating, and acute mood changes. If these occur, these effects do not last long (minutes to hours, but not day) and will resolve without need for treatment. There may be other risks that are currently unknown. The long-term effects of TMS are not known. There is also a risk of potential loss of confidentiality. Every effort will be made to keep your information confidential; however, this cannot be guaranteed.

While in the MRI scanner you may become too hot or too cold, in which case you may ask for an adjustment of room temperature or a blanket. Some people may become nervous or feel claustrophobic while in the scanner. If this happens, you may ask to be withdrawn and will be removed from the scanner immediately. A small number of people experience a sense of dizziness or vertigo while in the scanner due to the magnetic field. If this occurs and disturbs you, you may ask to be withdrawn and you will be removed immediately.

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.

There is always a chance that any research procedure can harm you. The research procedures in this study are no different. In addition to risks described in this consent, you may experience a previously unknown risk or side effect. If you experience any adverse events (a bad effect) after leaving the study, please contact Gopalkumar Rakesh MD, Assistant Professor, Department of Psychiatry at 859-382-7611 during regular business hours. If outside regular business hours, please contact the Psychiatry department On Call Group at (859) 226-7063 and explain to the physician that you are a study participant. For women of child-bearing potential: The risks of exposure to magnetic fields during pregnancy are unknown. Women of childbearing capacity will be asked to take a pregnancy test before exposure to MRI. You will be excluded from the study if the test indicates that you may be pregnant.

Risk	Ranking (rare/occasional/often)
Seizures	Rare
Hearing issues	Rare
Headache	Occasional
Syncope	Occasional
Dizziness/vertigo in scanner	Rare
Neck pain	Occasional

WILL YOU BENEFIT FROM TAKING PART IN THIS STUDY?

You may benefit from taking part in this study in helping you stop smoking. The study will inform us about how transcranial magnetic stimulation affects cognitive functions, visual attention, craving and impulsivity in people living with HIV.

IF YOU DON'T WANT TO TAKE PART IN THE STUDY, ARE THERE OTHER CHOICES?

If you do not want to be in the study, there are no other choices except not to take part in the study.

WHAT WILL IT COST YOU TO PARTICIPATE?

The University of Kentucky will not bill your insurance company, Medicare, or Medicaid for the study as it is done strictly for research. You will not incur any costs, should you decide to participate in this study.

WHO WILL SEE THE INFORMATION THAT YOU GIVE?

Every effort will be made to maintain the confidentiality of your study records. We will make every effort to prevent anyone who is not on the research staff from knowing that you gave us information, or what that information is. When we write about or share the results from the study, we will write about the combined information. We will keep your name and other identifying information private. All your personal details will be stored separate from all other research data in an encrypted format. Your identity will remain confidential, unless you give prior written approval or unless it is required by law. Your name, address and social security number will be listed on the receipt for payment that you receive, as required by the Internal Revenue Service (IRS); but no information about your participation in this research project will be released. The study will also be registered on www.clinicaltrials.gov and collective data on number of patients recruited into this trial will be reported on the website. To ensure the study is conducted properly, officials of University of Kentucky may look at or copy pertinent portions of records that identify you.

You should know that in some cases we may have to show your information to other people because of special circumstances. For example, the law may require us to share your information with:

- a court or agencies, if you have a reportable disease/condition.
- Authorities, if you report information about a child being abused; or if you pose a danger to yourself or someone else.

To help us protect your privacy, this research has a Certificate of Confidentiality. The researchers can use this Certificate to refuse to disclose information that may identify you to anyone not connected with this study, or in any legal proceedings. The exceptions to this rule are release of information:

- you have requested us to provide, for instance, to your insurance company or doctor;

- to the sponsor (e.g., National Institutes of Health) or agency auditing the research (e.g., Food and Drug Administration);
- about child or elder abuse, neglect, or harm to yourself or others; and
- about you if it involves a reportable disease.

This policy does not prevent you from releasing information about your own participation in this study.

CAN YOU CHOOSE TO WITHDRAW FROM THE STUDY EARLY?

You can choose to leave the study at any time. You will not be treated differently if you decide to stop taking part in the study. If you decide to withdraw from the study early, you will not receive any of the completion allowance described below. The data collected until that point of withdrawal from the study will remain in the study database and may not be removed. The study investigators can discontinue your participation for the following reasons: (1) if you verbally or physically assault another volunteer, patient or staff member at 245 Fountain Court; (2) if your behavior is disruptive to the other volunteers, patients, research staff or medical staff at 245 Fountain Court; (3) failure to comply with the alcohol, and drug use restrictions; (4) failure to comply with the pregnancy restrictions; (5) failure to complete a scheduled experimental sessions; (6) failure to perform the behavioral tasks to the best of your ability. If you are discharged from the study for any of these reasons, you will not receive the completion allowance described below. The medical doctor on this project can terminate your participation if he/she does not feel that it is medically safe for you to continue. If you experience intractable headaches with TMS, you can withdraw from the study with no ramifications to your clinic appointments. If your participation is terminated for medical reasons, you will receive the completion allowance for each of the sessions you completed.

ARE YOU PARTICIPATING, OR CAN YOU PARTICIPATE, IN ANOTHER RESEARCH STUDY AT THE SAME TIME AS PARTICIPATING IN THIS ONE?

You may take part in this study if you are currently involved in another research study. It is important to let the investigator/your doctor know if you are in another research study. You should discuss this with the investigator/your doctor before you agree to participate in another research study while you are in this study.

WHAT HAPPENS IF YOU GET HURT OR SICK DURING THE STUDY?

If you believe you are hurt or get sick because of something that is done in this study, you should immediately call Gopalkumar Rakesh MD, Assistant Professor, Department of Psychiatry at 859-382-7611. After business hours, please 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.

It is important for you to understand that 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 you get hurt or sick while taking part in this study. Also, the University of Kentucky will not pay for any wages you may lose if you are harmed by this study.

Medical costs related to your care and treatment because of study-related harm will be your responsibility. You do not give up your legal rights by signing this form.

WILL YOU RECEIVE ANY REWARDS FOR TAKING PART IN THIS STUDY?

You can receive up to a total of \$200 for taking part in this study. You will be paid \$50 for day one of the study, \$150 for day two of the study. If you choose to withdraw from the study after day one, you will still receive \$50 and an additional prorated amount depending on number of hours you spent in the study. You will not be compensated for the follow-up study visits. The final follow-up visit will be conducted during your regular clinic visit. There is a standard urine test conducted at the clinic, and the research team will take a few urine drops from the urine container to undergo the cotinine test.

With a few exceptions, study payments are considered taxable income reportable to the Internal Revenue Service (IRS). A form 1099 will be sent to you if your total payments for research participation are \$600 or more in a calendar year.

WHAT IF NEW INFORMATION WHAT IF NEW INFORMATION IS LEARNED DURING THE STUDY THAT MIGHT AFFECT YOUR DECISION TO PARTICIPATE?

We will tell you if we learn new information that could change your mind about staying in the study. We may ask you to sign a new consent form if the information is provided to you after you have joined the study.

WILL YOU BE GIVEN INDIVIDUAL RESULTS FROM THE RESEARCH TESTS?

The investigators on this project will share with you any significant new findings that may develop during the course of your participation. At that time, you will be allowed to decide if you wish to continue in the study. If you choose not to continue, you will receive the completion allowance for each of the visits you attended.

WILL WE CONTACT YOU WITH INFORMATION ABOUT PARTICIPATING IN FUTURE STUDIES?

The research staff would like to contact you in the future with information about participating in additional studies. If so, it will be limited to two times per year.

Do you give your permission to be contacted in the future regarding your willingness to participate in future research studies?

☐ Yes ☐ No Initials_____

WHAT ELSE DO YOU NEED TO KNOW?

Before you decide whether to accept this invitation to take part in this research study, please ask any questions now. Later, if you have questions about the study, you can contact the investigators directly at the phone numbers listed above. 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.

A description of the clinical trial will be available on ClinicalTrials.gov as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

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.

AUTHORIZATION TO USE OR DISCLOSE YOUR IDENTIFIABLE HEALTH INFORMATION

The privacy law, HIPAA (Health Insurance Portability and Accountability Act), requires researchers to protect your health information. The following sections of the form describe how researchers may use your health information.

The Researchers may use and share your health information with:

- The University of Kentucky's Institutional Review Board/Office of Research Integrity;
- Law enforcement agencies when required by law;
- University of Kentucky representatives;
- UK Hospital

- Food and Drug Administration

The researchers agree to only share your health information with the people listed in this document. Should your health information be released to anyone that is not regulated by the privacy law, your health information may be shared with others without your permission; however, the use of your health information may still be regulated by applicable federal and state laws.

You may not be allowed to participate in the research study if you do not sign this form. If you decide not to sign this form, it will not affect your:

- Current or future healthcare at the University of Kentucky;
- Current or future payments to the University of Kentucky;
- Ability to enroll in any health plans (if applicable); or
- Eligibility for benefits (if applicable).

After signing the form, you can change your mind and NOT let the researcher(s) collect or release your health information (revoke the Authorization). If you revoke the authorization:

- Send a written letter to: Gopalkumar Rakesh MD, Assistant Professor, Department of psychiatry, 2nd floor, 245 Fountain Court, Lexington 40509 to inform him of your decision.
- Researchers may use and release your health information **already** collected for this research study.
- Your protected health information may still be used and released should you have a bad reaction (adverse event).
- You will not be allowed to review the information collected for this research study until after the study is completed. When the study is over, you may have the right to access the information. The use and sharing of your information has no time limit.

If you have not already received a copy of the Privacy Notice, you may request one. If you have any questions about your privacy rights, you should contact the University of Kentucky's Privacy Officer between the business hours of 8am and 5pm EST, Monday-Friday at (859) 323-1184.

INFORMED CONSENT SIGNATURES

This consent includes the following:

- Key Information Page
- Detailed Consent

You will receive a copy of this consent form after it has been signed.

_____ Signature of research subject	_____ Date/Time
_____ Printed name of research subject	
_____ Printed name of [authorized] person obtaining informed consent	_____ Date/Time