Document Coversheet

Study Title: Accelerated Transcranial Magnetic Stimulation (TMS) for Smoking Cessation in People Living With HIV/AIDS (PLWHA)

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Consent to Participate in a Research Study

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

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 focusses 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 multiple sessions of non-invasive, non-significant risk transcranial magnetic stimulation influences the brain's decision-making process and visual attention in people living with HIV. 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 smoking versus neutral images. Your participation in this research will last 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. 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. You will also be asked to undergo brain MRI scans before and after the TMS session. The study will last three days.

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 four day 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. You must be living with HIV/AIDS to be in the 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			
Inhibitory Control Task (ABBA)	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 hs-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 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;
- 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 $350 for taking part in this study. You will be paid $50 for day one of the study, $100 for day two of the study and $ 50 for day three and day four of the study. If you choose to withdraw from the study after day one or two, you will still receive $50 or $150 respectively and an additional prorated amount depending on number of hours you spent in the study.

With a few exceptions, study payments are considered taxable income reportable to the Internal Review 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.

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**
_____ **Printed name of research subject**	
_____ Printed name of [authorized] person obtaining informed consent	_____ Date