UNIVERSITY OF PENNSYLVANIA
RESEARCH SUBJECT
INFORMED CONSENT AND HIPAA AUTHORIZATION FORM

Protocol Title:	Intensive TMS for Rapid Relief of Bipolar Depression Symptoms
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Emergency Contact:	Medical Emergency: please call 911 or present to your nearest emergency room Crisis Intervention: Crisis Response Center 215-829-5433
Funding Sponsor:	Milken Institute

Research Study Summary for Potential Subjects

You are being invited to participate in a research study. Your participation is voluntary, and you should only participate if you completely understand what the study requires and what the risks of participation are. You should ask the study team any questions you have related to participating before agreeing to join the study. If you have any questions about your rights as a human research participant at any time before, during or after participation, please contact the Institutional Review Board (IRB) at (215) 898-2614 for assistance.

The research study is being conducted to observe the effects of high dose spaced theta-burst rTMS (a form of transcranial magnetic stimulation) on depressive symptoms in individuals aged 18-70 with symptoms of bipolar depression who have failed (or not shown signs of improvement) after at least two prior treatments. Patients will be randomly allocated to one of two arms: active or sham (placebo/fake) TMS. The “sham” TMS treatment will mimic the sensory effects of TMS without actually stimulating the brain, allowing the “active” TMS treatment to be assessed objectively. There will be 50% chance that you will be randomized to real TMS and 50% to fake (placebo/sham) TMS. Neither you nor the TMS operator will know which type of TMS you are being given while participating. Disclosure of treatment assignment will only occur at the end of study participation.

If you agree to join the study, you will be asked to complete the following research procedures: clinical assessments with study staff, self-report questionnaires,

neurocognitive assessments, TMS administration, and Magnetic Resonance Imaging (MRI) scan procedures.

Your participation will last for approximately 6-8 weeks. Your participation includes 5 days of stimulation. This study may provide benefit to individual participants, even though not all participants are expected to equally benefit, if at all, from participating. This study may also further develop advancement of science.

The most common risks of participation are mild discomfort during the clinical interviews and assessments as well as physical discomfort and/or anxiety/claustrophobia during MRI. Common mild risks from TMS include: headache, local pain and discomfort, dizziness/nausea. More serious risks are rare but include seizures, worsening of depression symptoms, hearing loss, and burns form the coil for the TMS and injury from the MRI. Past research has shown no difference in increased risks with this stimulation schedule, as well as treatment efficacy. More detailed information about potential risks is included below.

You may discontinue participation in this study at any time with no loss of benefits you're otherwise entitled to. Alternatives to participation include not participating in this study and seeking treatment at traditional clinics and hospital spaces.

Please note that there are other factors to consider before agreeing to participate such as additional procedures, use of your personal information, costs, and other possible risks not discussed here. If you are interested in participating, a member of the study team will review the full information with you. You are free to decline or stop participation at any time during or after the initial consenting process.

Why am I being asked to volunteer?

You are being invited to participate in a research study because you are between the ages of 18 to 70, present symptoms of bipolar depression, and have failed or not shown signs of improvement after at least two prior treatments. Your participation is voluntary, which means you can choose whether or not you want to participate.

Your doctor may be an investigator in this research study. You do not have to participate in any research study offered by your doctor. If you choose not to participate, there will be no loss of benefits to which you are otherwise entitled. You may also decide to discuss the study with your family, friends, or family doctor. Being in a research study is different from being a patient. As an investigator, your doctor is interested both in your clinical welfare and in the conduct of this study.

If you decide to participate, you will be asked to sign this form.

What is the purpose of this research study?

The purpose of this study is to observe the effects of high dose spaced theta-burst rTMS (HDS-TBS) on depressive symptoms. This is a form of transcranial magnetic stimulation (TMS), which involves ten iTBS stimulation sessions/day on 5 days. TMS

has been an FDA-approved procedure for treatment-resistant depression since 2008. iTBS was recently approved by the FDA to be used to treat depression as well. This study administers the FDA-approved treatment schedule in a shorter amount of time, therefore it is considered an experimental schedule.

Recent studies suggest that higher resistance to treatment may require more stimulation in order to reduce symptoms of depression. Recent studies of iTBS applied over 5 days have shown that a decrease in the symptoms of depression are as good as when iTBS is given over 6 weeks. In this study we plan to have subjects receive iTBS over 5 days with multiple sessions per day rather than over a 6 week period.

How long will I be in the study?

Overall, this study is expected to go on for 1 year. If you take part in this study, your participation will last approximately 6-8 weeks, depending on scheduling availability.

Each visit will take the following approximate amount of time:

- Informed consent and clinical screening: 3-4 hours
- Baseline MRI and neurocognitive assessment: 2-3 hours
- TMS sessions: 10 15-minute sessions per day for 5 days within 7 or 10 days (10 hours per day), plus 30-minute clinical assessment and self-reports each day for 5 days
    - MRI on Day 2 or 3 of TMS treatment: 45-60 minutes (optional)
- Post stimulation MRI: 2-3 hours
- 4-week follow up visit: approximately 30 mins
- Optional Battleship Computer Task: Approximately 30 minutes

Please note that these times are approximates, some participants may take more time and some may take less time to complete these visits.

Regarding the stimulation sessions, you are asked to attend 10 sessions of stimulation per day, for five consecutive days. Each stimulation session will last approximately 10 minutes and will be spaced out 50 minutes from each other, for a total of at least 10 hours per day. We plan on starting the stimulation day around 8am and ending around 6pm. In between stimulation sessions, we will provide you with water and snacks and you will be able to leave the facility or stay in the waiting area, provided you return in time for the subsequent stimulation session. We will not provide meals.

We are asking 34 adults with treatment-resistant depression (at least 2 failed prior treatments) and a Bipolar Disorder diagnosis to participate in this study.

What am I being asked to do?

In order to test whether compressed iTBS stimulation works in treating refractory depression, each participant will undergo a Magnetic Resonance Imaging (MRI) scan. In order to test whether compressed iTBS stimulation works in treating bipolar depression, each participant will undergo a Magnetic Resonance Imaging (MRI) scan. The images from the scan will be analyzed to pinpoint a specific area of the brain where

TMS is predicted to produce the greatest reduction in symptoms. After this, participants are randomly assigned to sham (placebo) or active TMS, both of which include 5 days of stimulation. “Sham” TMS treatment will mimic the sensory effects of TMS without actually stimulating the brain, allowing the “active” TMS treatment to be assessed objectively.

Please refer below for a more specific description of study procedures

- Clinical assessments with Study Staff: regarding your thoughts, feelings, and behaviors.
- Self-report Questionnaires: regarding your thoughts, feelings, and behaviors.
- Neurocognitive Assessments: Completed on an electronic tablet or computer. This involves doing a variety of activities that test areas of brain cognition, such as memory, concentration and attention.
- TMS: For transcranial magnetic stimulation (TMS), a wire coil is held on the scalp. For this procedure, you sit down on a chair and will be asked to wear ear plugs as well as a swim cap that will hold the coil tracker, to ensure the stimulation site remains consistent. The use of swim cap is to increase your comfort of fit of the coil tracker, as well as ease the maneuverability of the TMS coil. A brief electrical current passes through the coil and creates a magnetic pulse that stimulates the brain. You will hear a click and may feel a pulling sensation on the skin under the coil. There may be a twitch in muscles of the face, arm or leg. We may ask you to tense certain muscles or perform simple actions or tasks during TMS. TMS intensity will be calibrated specifically for your brain. To determine the stimulation level, we will place the coil over the part of the brain that controls movement. We will then adjust the intensity of the stimulation until it causes your finger to have a small twitch. This calibration is done to ensure that sufficient stimulation intensity is used for each individual without excessive stimulation. You will be randomly assigned to either active or sham (placebo) TMS group. There will be a 50% chance that you will be randomized to real TMS and 50% to sham (placebo/fake) TMS. Neither you nor the TMS operator will know which type of TMS you are being given while participating. Disclosure of treatment assignment will only occur at the end of study participation.
- Magnetic Resonance Imaging (MRI) Scan: an MRI uses electromagnetic radio waves in a strong magnetic field to take clear pictures of your brain. These pictures will help us identify the precise location of your TMS target. In other words, exactly where the TMS should be administered on your head. You will be asked to lie still on a table in the MRI machine for two 1-hour scans.

If you decide to participate, in case you are undergoing another type of treatment, you will be able to continue with your current treatment regimen. In case we are unsure about your participation, we may contact your treatment provider (i.e. psychologist, nurse practitioner, psychiatrist) to gather additional information to make a determination.

What are the possible risks or discomforts?

You may experience one or more of the risks indicated below from being in this study. In addition to these, there may be unknown risks, or risks that we did not anticipate, associated with being in this study.

iTBS &TMS. This study utilizes two forms of Transcranial Magnetic Stimulation (TMS): intermittent Theta Burst Stimulation (iTBS) & single pulse TMS. TMS is a FDA-approved non-invasive brain stimulation technique for a variety of diagnoses. iTBS was recently approved by the FDA to be used to treat depression as well. As with any technique, there may be long-term risks due to TMS that are currently unknown. The most common side effect of TMS (approximately 25% of subject) is a mild headache. There are no known long-term adverse effects reported with the use of this device. Rarely, device malfunction could result in a scalp burn (less than 1% of subjects).

- **Certain Medical Diagnoses**: for subjects with epilepsy, activation of the brain by TMS could also activate a seizure. Subjects with stroke may be at increased risk for a seizure due to the brain scarring. For these reasons, anybody with history of epilepsy or stroke will be excluded from the study. For a typical physically healthy person, a TMS-induced seizure in this experiment is very unlikely.
- **Noise**: the TMS device produces a clicking sound. To minimize this possibility, you will be given protective earplugs or headphones.
- **Nausea**: although it is uncommon, approximately 5% of subjects have experienced nausea during the experiment. You can discontinue the experiment if you experience any discomfort during the study.
- **Mild Swelling or Bruising**: You may also experience temporary and local bruising, swelling, or pain from the swim cap and/or muscle activation by TMS.

Accelerated iTBS. Present research about increased iTBS frequency (Li et al., 2014; Williams et al., 2018) does not suggest any increased risk of side effects due to the increased treatment frequency. Current research also shows no significant difference between accelerated and conventional TMS treatment schedules (Blumberger et al., 2017). That being said, you will be monitored for worsening of depressive symptoms or side effects. If you experience worsening of depressive symptoms (i.e. increased insomnia, increased negative thoughts, increased suicidality), you will be referred to the study physician and/or to research study staff for further evaluation and possible next steps. If that occurs, research study staff and PI can refer to additional resources as necessary.

Clinical assessments and self-report questionnaires. Some discomfort may be associated with the clinical assessments and self-report questionnaires conducted in this study. You may experience emotional discomfort when answering some questions in the questionnaires or when talking about personal information. You may choose not to answer any of the questions and to terminate your participation.

MRI Scan.

- **Claustrophobia**: You may experience claustrophobia (fear of enclosed spaces and/or anxious feelings accompanied by fast heart rate or shortness of breath)

within the MRI scanner. A MRI scan requires you to be in a partially enclosed space inside the scanner. Some people may find this to be uncomfortable and claustrophobic. You need to inform the doctor ordering the scan, or the study staff, if you suffer from claustrophobia.

- **Magnetic Fields**: There is no known health risk associated with exposure to magnetic fields during an MRI. There are minimal risks from the loud noise associated with the MRI scanner and from the discomfort of lying on a hard surface. We shall provide you with protective earplugs as necessary and make every attempt to ensure your comfort with blankets, etc. during your time in the scanner.
- **Flying Objects**: The greatest risk of MRI is a magnetic object flying through the air toward the magnet and hitting you. To reduce this risk we require that all people involved with the study remove all magnetic metal from their clothing and all magnetic metal objects from their pockets. No magnetic metal objects are allowed to be brought into the magnet room at any time except by approved personnel. In addition, once you are in the magnet, the door to the room will be closed so that no one inadvertently walks into the room.
- **Medical Implants and Foreign Bodies**: There is also a potential risk of MRI for subjects with medical implants or other metallic objects in their body. All subjects undergoing MRI scanning must complete a screening evaluation risk in advance of the study for the presence of medical implants or other foreign bodies that could pose an injury. Every effort will be made to insure that disclosed implants or foreign bodies do not pose a risk to subjects. In cases where there is insufficient information to evaluate the risks associated with an implant or foreign body, the MRI study will not be allowed to proceed.
- **Pregnancy**: Although there are no known risks related to MRI on pregnant women or a fetus, there is a possibility of yet undiscovered pregnancy related risks. Since there is no guarantee that patients will receive active TMS treatment or that patients will directly benefit from the TMS, we will exclude pregnant women.
- **Incidental Findings Clause**: This MRI is not a clinical scan. It is possible that during the course of the research study, the research staff may notice an unexpected finding(s). Should this occur, the finding(s) will be considered by the appropriate personnel and the PI will inform you if necessary. These possible finding(s) may or may not be significant and may lead to anxiety about your condition and to further work-up by your physician.

Worsening of Depression Symptoms. While participating in this study, your care will be managed by the research team and attending physician. You will be asked to complete assessments about your thoughts, feelings, and behaviors. In the event that during the course of this investigation your symptoms worsen to the point where you feel you need psychological or medical support, please communicate your situation to the present research staff and/or attending physician. There are no known risks of worsening suicidal ideation following TMS application, instead the purpose of TMS application is to lessen these symptoms. If you were to experience suicidal ideations,

please refer to the attending research team members and physician. In case of emergency, please present to the nearest emergency room or call 911.

If your symptoms require urgent attention, please call 911 and present to your nearest emergency room or contact: Philadelphia Behavioral Health week at (215) 686-4420. PBH hotlines are staffed 24 hours a day, 7 days per week. For similar hotlines outside of the Philadelphia area, please consult www.suicide.org.

Risk to confidentiality. There is a rare risk that confidentiality could be breached in this study. Breaches in confidentiality could impact your future insurability and/or employability.

What if new information becomes available about the study?

During the course of this study, we may find more information that could be important to you. This includes information that, once learned, might cause you to change your mind about being in the study. We will notify you as soon as possible if such information becomes available.

What are the possible benefits of the study?

There is no guarantee that you will benefit from participation in this study. Chronically bipolar depressed subjects may benefit from a reduction of symptoms from the iTBS. It is hoped that information gained from this study will add to the body of knowledge about the management of depression and bipolar disorders.

What other choices do I have if I do not participate?

This is a voluntary study. If you choose not to participate, there will be no loss of benefit to you. If you do not participate in this study, you can discuss other options for care with your physician. Alternatives to participation include seeking treatment at traditional clinics and hospital spaces.

Will I be paid for being in this study?

You will be compensated $75 for completion of this study. Your payment will be given to you in the form of a Greenphire ClinCard. This is a reloadable prepaid card (similar to a debit/credit card) that allows funds to be available immediately. Please note that payments of $100.00 or more may take up to 1 full business day to appear available on your ClinCard. You can use it for in-store or online purchases by selecting the “Credit” option at check-out, or it can be cashed out by presenting to a teller at any MasterCard member bank (look for a MC logo on the bank window). Study staff will provide you with a “ClinCard Cardholder FAQ: US” document to help answer any questions you may have.

Please note: In order to be compensated for your participation in this study, you must provide your Social Security Number. Additionally, the University of Pennsylvania is required to report to the IRS any cumulative payments for participation in research studies that exceed a total of $600 in a calendar year.

Will I have to pay for anything?

You will not have any costs for participating in this research study. The administration of all study-related procedures will be covered by the study.

What happens if I am injured from being in the study?

We will offer you the care needed to treat injuries directly resulting from taking part in this research. We may bill your insurance company or other third parties, if appropriate, for the costs of the care you get for the injury, but you may also be responsible for some of them.

There are no plans for the University of Pennsylvania to pay you or give you other compensation for the injury. If you feel this injury was caused by medical error on the part of the study doctors or others involved in the study, you have the legal right to seek payment, even though you are in a study. You do not give up your legal rights by signing this form.

If you think you have been injured as a result of taking part in this research study, tell the person in charge of the research study as soon as possible. The researcher's name and phone number are listed in the consent form.

When is the Study over? Can I leave the Study before it ends?

This study is expected to end after all participants have completed all visits, and all information has been collected. This study may also be stopped at any time by your physician, the study Sponsor, or the Food and Drug Administration (FDA) without your consent because:

- The Primary Investigator feels it is necessary for your health or safety. Such an action would not require your consent, but you will be informed if such a decision is made and the reason for this decision.
- You have not followed study instructions.
- The Sponsor, the study Principal Investigator, or the Food and Drug Administration (FDA) has decided to stop the study.

If you decide to participate, you are free to leave the study at anytime. Withdrawal will not interfere with your future care.

How will my personal information be protected during the study?

We will do our best to make sure that the personal information obtained during the course of this research study will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law.

An exception to confidentiality is if you report child abuse or neglect or if you report suicidal or homicidal ideation or intent to the research team. Any information about child abuse or intent to harm yourself or others will be reported to authorities, as required by law.

If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. The Institutional Review Board (IRB) at the University of Pennsylvania will have access to your records. If this study is being overseen by the Food and Drug Administration (FDA), they may review your research records.

Once hard copy records are collected for the study, they will be kept in a double-locked environment. Data collected during the study will be entered and stored in a password-protected database, accessible only to engaged study members. All electronic data will be coded and assigned a randomly generated research identification number. If we write a report or article about this study or share the study data set with others, we will do so in such a way that you cannot be directly identified.

Will information about this study be available to the public?

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

What may happen to my information collected on this study?

Future Use of Data

Your information will be de-identified by assigning a unique identifier number to all your collected data. Identifiers will be retained with study records, but will be recorded in a password-protected document and not shared. De-identified means that all identifiers have been removed. The information could be stored and shared for future research in this de-identified fashion. The information may be shared with other researchers within Penn, or other research institutions, as well as pharmaceutical, device, or biotechnology companies. It would not be possible for future researchers to identify you as we would not share any identifiable information about you with future researchers. This can be done without again seeking your consent in the future, as permitted by law. The future use of your information only applies to the information collected on this study.

Electronic Medical Record and Release of Study Related Information

What is an Electronic Medical Record?

An Electronic Medical Record (EMR) is an electronic version of your medical chart within a health system. An EMR is simply a computerized version of a paper medical record.

For the purpose of this study, we will not utilize Penn Medicine healthcare related services and will not create or edit your EMR.

What may be placed in the EMR?

For the purpose of this study, we will not utilize Penn Medicine healthcare related services and will not create or edit your EMR. None of the information related to this study will be in the EMR.

Will I receive the results of research testing that may be relevant to my health?

Many of tests done in research studies are only for research and have no clear impact on your healthcare. Research results for this study will not be returned to you because they would not be relevant to your healthcare. As discussed in the MRI scan risks section above, it is possible that during the course of the research study, the research staff may notice an unexpected finding(s). Should this occur, the finding(s) will be considered by the appropriate personnel and the PI will inform you if necessary. These possible finding(s) may or may not be significant and may lead to anxiety about your condition and to further work-up by your physician.

What information about me may be collected, used or shared with others?

Protected Health Information (PHI) is health information that identifies you. PHI is protected by federal law under HIPAA (the Health Insurance Portability and Accountability Act). To take part in this research, you must give the research team permission to use and disclose (share) your PHI for the study as explained in this consent form. During your participation, you will be asked to provide your name, address, telephone number, email address, and date of birth. You will also be asked about your medical history as it relates to this study.

Why is my information being used?

Your information is used by the research team to contact you during the study. Your information and results of tests and procedures are used to:

- do the research
- oversee the research
- to see if the research was done right
- to evaluate and manage research functions.

Where may my information be stored?

Information related to your participation in clinical research will be contained in a clinical trial management system (CTMS). A clinical trial management system (CTMS) is used to register your information as a participant in a study. This allows for your research data to be entered and stored for the purposes of study operational and financial applications and other activities required as part of the conduct of the research. Once placed in the CTMS your information may be accessible to other authorized personnel at Penn Medicine that support research operations. Your information may be held in other research databases.

Who may use and share information about me?

The following individuals may use or share your information for this research study:

- The investigator for the study and the study team
- Other authorized personnel at Penn Medicine and the University of Pennsylvania, including offices that support research operations

- Other research personnel with access to the databases for research and/or study coordination and as otherwise approved by the IRB

Who, outside of Penn Medicine, might receive my information?

The following individuals may use or share your information for this research study:

- Other research personnel or collaborators as authorized, even if they are not part of Penn Medicine
- The funding sponsor and organizations supporting the sponsor
- The necessary oversight organizations and regulatory authorities

Once your personal health information is disclosed to others outside Penn Medicine, it may no longer be covered by federal privacy protection regulations.

The Principal Investigator or study staff will inform you if there are any additions to the list above during your active participation in the trial. Any additions will be subject to Penn Medicine procedures developed to protect your privacy.

How long may Penn Medicine use or disclose my personal health information?

Your authorization for use of your personal health information for this specific study does not expire.

However, Penn Medicine may not re-use or re-disclose information collected in this study for a purpose other than this study unless:

- You have given written authorization
- The University of Pennsylvania's Institutional Review Board grants permission
- As permitted by law

Can I change my mind about giving permission for use of my information?

Yes. You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the investigator for the study. If you withdraw your permission, you will not be able to stay in this study.

What if I decide not to give permission to use and give out my health information?

Then you will not be able to be in this research study.

You will be given a copy of this Research Subject HIPAA Authorization describing your confidentiality and privacy rights for this study.

By signing this document, you are permitting Penn Medicine to use and disclose personal health information collected about you for research purposes as described above.

Who can I call with questions, complaints or if I'm concerned about my rights as a research subject?

If you have questions, concerns or complaints regarding your participation in this research study or if you have any questions about your rights as a research subject, you should speak with the Principal Investigator listed on page one of this form. If a member of the research team cannot be reached or you want to talk to someone other than those working on the study, you may contact the IRB at the number on page one of this form.

Do you agree to be contacted for future studies by the Center for Neuromodulation of Depression and Stress?

☐ Yes ☐ No

_____ _____
Initials Date

When you sign this form, you are agreeing to take part in this research study. This means that you have read the consent form, your questions have been answered, and you have decided to volunteer. Your signature also means that you are permitting the University of Pennsylvania to use your personal health information collected about you for research purposes within our institution. You are also allowing the University of Pennsylvania to disclose that personal health information to outside organizations or people involved with the operations of this study.

A copy of this consent form will be given to you.

_____ _____
Name of Subject (Please Print) Signature of Subject Date

_____ _____
Name of Person Obtaining Consent (Please Print) Signature Date