Title: Testing a Neurocognitive Model of Distancing Using Transcranial Magnetic Stimulation

Duke University IRB Protocol: Pro00100171

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Study Protocol and Statistical Analysis Plan

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Research Summary

1. **Protocol Title:** Testing a neurocognitive model of distancing using transcranial magnetic stimulation

2. **Purpose of study:** Distancing is a type of cognitive emotion regulation that relies on self-projection, or the ability to shift perspective from the here and now to a simulated time, place, or person.[1] Based on our own review and meta-analysis of the distancing literature, we have developed a model of the neurocognitive processes of distancing,[2] which are currently not well understood.[3] The goal of this project is to test specific neurocognitive relationships from this model using transcranial magnetic stimulation (TMS). This testing will serve the broader purpose of improving scientific knowledge regarding the neural bases of 1) cognitive emotion regulation and 2) simulating and shifting perspectives in healthy adults. Additionally, it will assess the feasibility of modulating emotion regulation performance via constituent processes of distancing using TMS in healthy adults.

Primary Objective: Test the causal influence of cortical brain areas on the cognitive processes of distancing as defined in our model.
Measurement: We will apply TMS to cortical targets to modulate local neural activity during performance of a distancing task. The effect of stimulation will be evaluated by contrasting distancing performance with active stimulation against distancing performance with sham stimulation for each participant. Distancing performance will be assessed through self-reported valence, matching our previous studies of distancing and others in the literature.[4,5] The cognitive specificity of the stimulation effect will be evaluated by contrasting distancing performance with performance on a control task that differs by the target cognitive process.

Secondary Objective: Establish the feasibility of modulating emotion regulation performance using TMS on novel cortical targets and cognitive mechanisms.
Measurement: We will apply TMS to cortical targets to modulate local neural activity during performance of a distancing task. The effect of stimulation will be evaluated by contrasting distancing performance with active stimulation against distancing performance with sham stimulation for each participant. Distancing performance will be assessed through self-reported valence, matching our previous studies of distancing and others in the literature.[4,5]

3. **Background & Significance:** Distancing is an effective type of cognitive emotion regulation.[6-8] While some work has explored which areas of the brain are involved in distancing,[4,9,10] the ways in which the cognitive processes of distancing relate to these areas is not clear. By performing a review of the distancing literature and meta-analysis of fMRI studies of distancing, we have developed a preliminary model of these neurocognitive relations.[2] This model serves as a basis for generating testable hypotheses with methods capable of modulating brain function. TMS is an ideal method for this work given its capacity to modulate activity locally, temporarily, and non-invasively,[11] and it is already being explored as a tool for modifying affective processes.[12] These previous efforts have largely focused on the dorsolateral prefrontal cortex though, and reports on the effectiveness of these efforts have varied.[13] These limitations underscore the need for new and effective stimulation paradigms. Our model identifies novel targets and mechanisms for modulating cognitive emotion regulation. Specifically, we hypothesize the left temporoparietal junction (TPJ) to be critically involved in managing the multiple perspectives necessary for self-projection and distancing. By using TMS to disrupt activity in this area, we can simultaneously test one of the key components of our model of distancing and the potential of this cortical area as a target for modulating emotion regulation performance.

4. Design & Procedures: For previous studies, we have developed a task to elicit and assess distancing performance. We will adapt this task for the current project. The basic structure of a trial is depicted in Figure 1.

Figure 1

Aversive pictures from the International Affective Pictures System[14] are used to elicit negative emotional responses. While viewing a picture, the participant either attempts to minimize any emotional response by taking the perspective of a neutral, objective observer (distancing condition), or allows emotional responses to develop naturally (passive control condition). After the regulation period, the participant rates his or her affective state using a valence scale, and for distancing trials, perceived effort expended during regulation. Distancing performance is assessed for each participant by subtracting the average valence rating on natural response trials from distancing trials, yielding the shift toward less negative/more positive valence resulting from regulation. In addition to these two trial types, trials are included in which the participant is cued to respond naturally to positive pictures. These trials are not analyzed, but they reduce predictability in the task and the likelihood of negative mood induction. Finally, trials are included in which participants are cued to regulate negative responses using a distraction technique that is not expected to rely on self-projection or the targeted brain area.[15,16] For this technique, participants are instructed to silently rehearse a previously learned nine-digit number while viewing the picture. This condition allows for the assessment of whether stimulation-induced effects on distancing performance are related to a process specific to distancing (i.e. self-projection) or processes related to cognitive emotion regulation more generally (e.g. cognitive control, affective self-reflection).

We will use an offline stimulation protocol to disrupt activity in the target area. Specifically, we will employ a continuous theta-burst stimulation (cTBS) sequence using a figure-8 coil positioned tangentially to the scalp over the target coordinates.[17] The cTBS procedures and devices follow those of approved Duke Health IRB Protocol Pro00066383. We have defined the target coordinates for stimulation (MNI -53, -53, 23) based on peak objective distancing activation in the left TPJ in our previous fMRI study using the same task. In order to target the standard-space coordinates, we will collect a structural MRI scan for each participant and compute a registration between the standard MNI brain space and each individual's brain. The cTBS sequence we will use is a standard protocol, and we will not deviate from the established parameters.[17] This sequence allows for a short stimulation period of 20 seconds with a disruptive effect to local cortical activity estimated to subside 20-30 minutes post-stimulation.[17,18] Thus, we hypothesize that cTBS to the TPJ immediately before the task will depress local activity and impair performance on the distancing task.

A diagram of the full study design is shown in Figure 2. Initial prescreening will be used to determine eligibility based on safety indications for MRI and TMS, with full screenings following on the days of the respective procedures. In addition to the MRI scan, the Day 1 session will include a thorough training session (approx. 25 minutes) for the experimental task based on our previous distancing research protocols. Participants will return a few days after the Day 1 session to complete the main experimental session. After completing a brief training refresher for the experimental task, we will calibrate the stimulation intensity for each participant by determining his or her active motor threshold (see below). Each pulse of the cTBS sequence will then be delivered at 80% of the estimated active motor threshold, following standard procedure for cTBS.[17] We will use a within-subjects design in which each participant receives both active

stimulation and an electrical sham stimulation designed to resemble the scalp sensations of TMS. As indicated in Figure 2, participants will complete one run of the task after each stimulation condition in a counterbalanced design, allowing enough time for stimulation effects to subside between conditions. Participants will also complete a simplified version of the task ("baseline" in Figure 2) designed to briefly estimate the regulation effect of objective distancing at different times throughout the session to confirm that any stimulation-related effects on self-projection have subsided. Finally, participants will be debriefed to assess awareness of stimulation conditions and proper use of techniques during the experimental task.
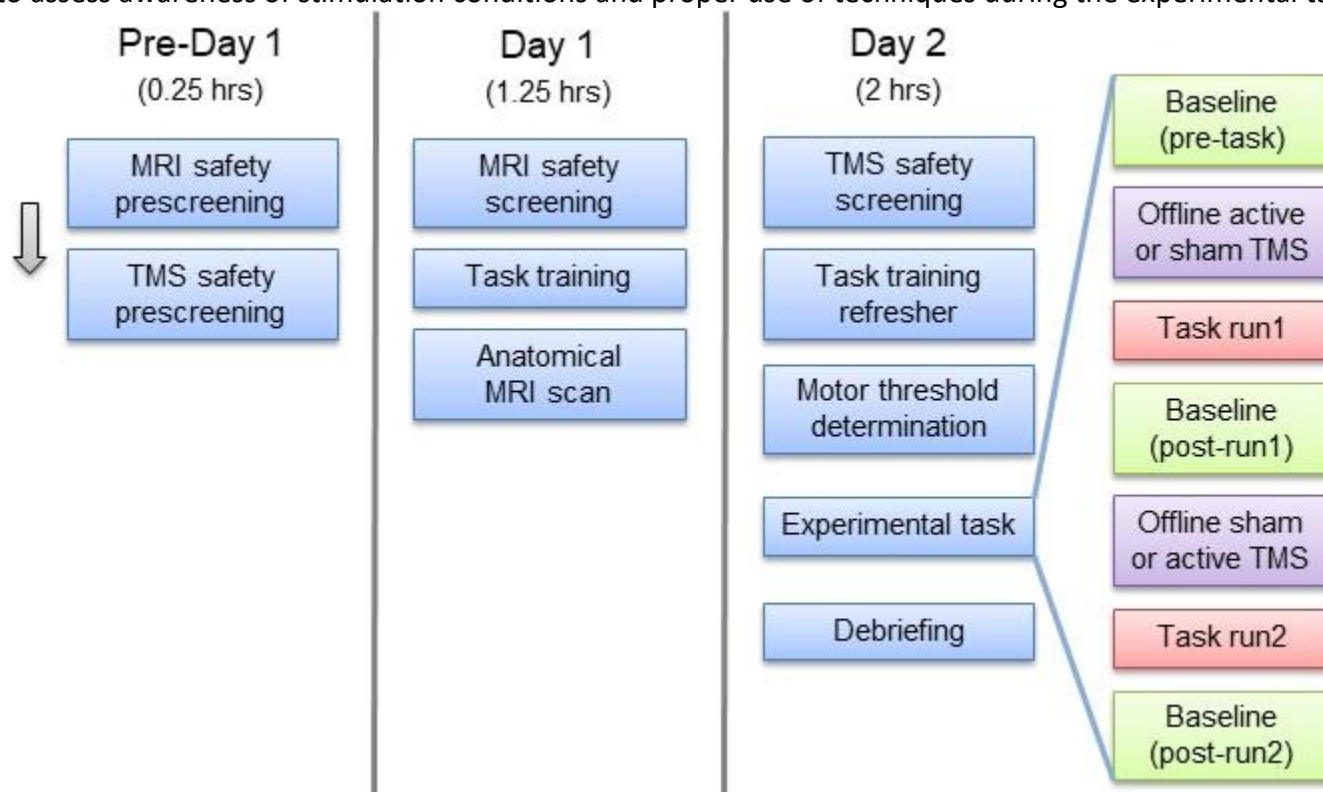
Pre-Day 1 (0.25 hrs)	Day 1 (1.25 hrs)	Day 2 (2 hrs)	
MRI safety prescreening	MRI safety screening	TMS safety screening	Baseline (pre-task)
TMS safety prescreening	Task training	Task training refresher	Offline active or sham TMS
	Anatomical MRI scan	Motor threshold determination	Task run1
		Experimental task	Baseline (post-run1)
		Debriefing	Offline sham or active TMS
			Task run2
			Baseline (post-run2)

Figure 2.

One hundred healthy young adults (18-39 y.o.) will participate in all parts of the experiment. Participants will have no history of psychiatric or neurological illness and no ongoing psychoactive drug use (for more details see Section 5 below). Normal right-handed volunteers will be recruited from a registry maintained by the Duke Brain Imaging and Analysis Center under Pro00010672, *Screening for Participation in MRI Subject Pool*.

Screening: Participants will complete screening via a REDCap survey to determine eligibility for the study. This survey will include demographic and medical questions to evaluate the inclusion and exclusion criteria for the study including safety contraindications for MRI or TMS. Additionally, participants will complete the BIAC MRI safety screening form and urine pregnancy test (female participants) at the first study appointment before MRI procedures and the TMS adult safety screening form, urine pregnancy test (female participants), and urine drug test at the second study appointment before TMS procedures.

Motor Threshold Determination: All TMS procedures will occur in room 54211 in the Department of Psychiatry and Behavioral Sciences, Duke Clinic South. Motor threshold (MT) is defined as the minimum magnetic flux needed to elicit a threshold EMG response in a target muscle with 50% probability. MT is the standard in the field for determining the intensity of TMS for each individual to reduce seizure risk. The motor evoked potentials (MEP) for the contralateral first dorsal interosseus muscle will be measured with EMG. The scalp region producing the largest amplitude MEP will be identified. At that scalp location, the

lowest TMS intensity able to elicit an MEP of ≥200µV in peak-to-peak amplitude with 50% probability will be determined, using an adaptive threshold hunting procedure.[19] The adaptive threshold hunting procedure is a semi-automated algorithm for estimating the MT with a minimal number of trials. MT will be determined for the left hemisphere with the muscle contracted at 20% of maximum voluntary contraction (verified by a pinch gauge dynamometer). Estimating MT during voluntary muscle contraction is standard procedure for cTBS protocols.[20,21] Individual MT will be used to determine the intensity of stimulation for each individual, following standard procedure for cTBS.[17]

5. **Selection of Subjects:** Subjects will be healthy adults who are appropriate research participants.

   Study Inclusion Criteria:
   1. Age between 18-39 years inclusive
   2. Willing to provide informed consent
   3. English speaking
   4. Signed HIPAA authorization

   Study Exclusion Criteria (ascertainment when appropriate):
   1. Current or recent (within the past 6 months) substance abuse or dependence, excluding nicotine and caffeine (assessed via urine test).
   2. Current serious medical illness.
   3. History of seizure except those therapeutically induced by ECT (childhood febrile seizures are acceptable and these subjects may be included in the study), history of epilepsy in self or first degree relatives, stroke, brain surgery, head injury, cranial metal implants, known structural brain lesion, devices that may be affected by TMS or MRI (pacemaker, medication pump, cochlear implant, implanted brain stimulator) [assessed via TMS Adult Safety Screening form].
   4. Subjects are unable or unwilling to give informed consent.
   5. Diagnosis of any DSM-V disorder.
   6. Diagnosis of any clinically defined neurological disorder including, but not limited to:
      a. Any condition likely to be associated with increased intracranial pressure
      b. Space occupying brain lesion.
      c. History of stroke.
      d. Transient ischemic attack within two years.
      e. Cerebral aneurysm.
      f. Dementia.
      g. Parkinson's disease.
      h. Huntington's disease.
      i. Multiple sclerosis.
   7. Increased risk of seizure for any reason, including prior diagnosis of increased intracranial pressure (such as after large infarctions or trauma), or currently taking medication that lowers the seizure threshold.
   8. Subjects not willing to tolerate the confinement associated with being in the MRI scanner.
   9. Women who are pregnant or breast-feeding (assessed via urine test).
   10. Blindness.
   11. Inability to read or understand English.
   12. Intracranial implants, such as:
      a. Cochlear implants;
      b. Aneurysms clips;
      c. Shunts;
      d. Stimulators;

      e.   Electrodes;
      f.   Cardiac pacemakers;
      g.   Vagus Nerve stimulation devices.

6. **Subject Recruitment & Compensation:** One hundred healthy volunteers will be recruited through IRB-approved advertising. Participants will participate in both sessions of the experiment. Volunteers will be recruited via a registry maintained by the Duke Brain Imaging and Analysis Center under Pro00010672, *Screening for Participation in MRI Subject Pool*.

All subjects will be compensated for each study visit at $20 per hour of participation. Subjects who pay for parking for a visit will be paid $2 per hour to reimburse parking fees.

7. **Consent Process:** All individuals participating in this study will go over the informed consent forms with at least one researcher from the lab that has undergone training on the task by the Primary Investigator and has completed Human Subjects Research Training. Obtaining consent will always occur at a private setting with just the researcher and the participant, who will have sufficient time to read the forms carefully. The researcher will also answer any questions asked by the participant at this time concerning the study and his or her participation. After that, participants will be asked to initial, sign, and date the form where needed. In addition a copy of the informed consent form will be given to the subject for their records. Subjects unable to give a binding informed consent will not be allowed to proceed in the study.

8. **Subject's Capacity to Give Legally Effective Consent:** This study involves healthy volunteers who are not decisionally impaired. Only individuals capable of consent will be enrolled in the consent process.

9. **Risk/Benefit Assessment:** There are no known long-term health risks to the use of MRI when operated within FDA guidelines. However, there are safety concerns posed by the strong magnetic fields used to make images collected with MRI. All scans conducted under this protocol meet the FDA's guidelines for non-significant risk for static field strength, specific absorption rate (SAR), time varying magnetic fields (dB/dt), and acoustic noise.

    There are no known long-term health risks to the use of TMS per se when operated within consensus safety guidelines.[20] In 2008, the FDA approved the use of high frequency TMS in the treatment of depression. Also in 2008, an international consensus conference on safety guidelines for TMS met. Their report systematically reviewed the thousands of healthy subjects and patients who have undergone TMS in order to allow for a better assessment of relative risks.[20] The relative infrequency of adverse events using TMS 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 TMS 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). This consensus safety report went on to suggest safety guidelines based on the now extensive international experience with repetitive TMS (rTMS). These guidelines include the rTMS intensity and timing parameters considered safe as well as standard training and planning for managing emergencies. While this report did not include specific safety guidelines for the parameters of cTBS, this report was referenced by a later report on the safety of cTBS,[21] which found that "both the reported symptoms and general risk of adverse events during TBS is comparable to or less than other high frequency rTMS protocols."

    So far, there has only been one report of seizure occurrence with TBS.[22] In this case, cTBS was conducted in a healthy 33-year-old male with no seizure risk factors. The stimulation intensity used was 100% resting

MT, which is significantly higher than the standard cTBS protocol.[17] We will use the standard cTBS intensity level in the present study, which is much lower and at which no seizures have been reported. The systematic review of the safety of TBS reported that over 1000 individuals have participated in more than 4500 sessions using TBS.[21] Since that review, no seizures have been reported. Thus far, the risk of seizure induction by TBS is low and the crude risk of seizure per session of TBS is estimated to be 0.02%.[21]

Participation is voluntary, and there will be no pressure or time constraints regarding the decision to participate. There are no benefits to the participants except for the monetary reward or compensation, as well as the good will of helping the progress of scientific research.

MRI Adverse Events Plan:

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 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.

TMS Adverse Events Plan:

Seizure is a theoretical risk with TMS. In the Rossi et al. report[20] it was stated that "The occurrence of seizures has been extremely rare, with most of the few new cases receiving TMS 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 TMS sessions over the last two decades) of seizure related to TMS have been reported. Eight occurred before safety parameters were established in 1997. Of the other eight reports, six occurred either when the safe TMS 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 in 1996, researchers in the field agreed upon a set of *TMS consensus safety guidelines*, including recommended stimulation parameters and contraindications,[23] and these consensus guidelines have been recently updated.[20] Widespread adherence to the 1996 guidelines has resulted in the virtual elimination of inadvertent seizures in TMS studies.[20] Specific safety guidelines for cTBS have not been established, but a safety review of the many studies performed using a standard cTBS protocol (as in the current study) found the reported symptoms and risk of adverse events to be comparable to or less than other forms of repetitive TMS.[21]

We will screen subjects for known risk factors for seizure with TMS (medical screening and medical history). Personnel who administer TMS are trained to recognize a potential seizure event and to act as "first responders" in order to administer appropriate initial care. These study personnel have undergone Basic Life Support 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 the medical center's emergency phone line. 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.

The most commonly reported side effect of TMS 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.

Syncope is considered a rare side effect of TMS and has been reported in individuals who faint during blood draws. If a participant should experience syncope, he or she will be withdrawn from the study and the participant's blood pressure will be monitored until it returns to a healthy level.

As noted in Rossi et al.,[20] Loo and colleagues reported mild and transient changes in auditory threshold in two depressed patients following a 2-4 week course of TMS.[24] Cases of tinnitus have been reported after TMS treatments. In addition, in a study investigating the effects of TMS on symptoms of depression, a patient experienced moderate to severe tinnitus after an TMS session in which earplugs were not used. Rossi et al. recommended that hearing protection always should be worn during TMS application, and that individuals with cochlear implants not receive TMS. In the current study, earplugs will be worn by all subjects during TMS procedures. Individuals with cochlear implants will be excluded from participation.

Risks to the unborn children of pregnant women receiving MRI and TMS are unknown. Pregnant women will be excluded as per IRB policy. Female subjects are tested with a urine pregnancy test prior to their first MRI session as per IRB-approved BIAC policy. The person(s) who will perform the urine pregnancy test will have successfully completed training as directed by the Chair of Obstetric and Gynecology of the Duke University School of Medicine. The urine pregnancy test kits used for this research study will be those commercially available test kit specified by the Chair of Obstetric and Gynecology and in routine use at DUHS.

10. Costs to the Subject: There is no cost for subjects to participate in this study.

11. Data Analysis & Statistical Considerations: The primary outcome measure of this study is change in self-reported valence. Specifically, we will compute the difference in mean valence scores between distancing trials and natural response trials. This difference represents the change in valence due to distancing, or its emotion regulatory effect, and this metric has been sensitive to distancing manipulations in our previous experiments. We hypothesize that this difference will be reduced following active TMS relative to sham TMS. We will compute similar analyses for distraction trials relative to natural response trials, hypothesizing no effect of stimulation condition in this case. We will apply repeated-measures analyses of variance with appropriate follow-up tests to conduct these analyses.

A secondary outcome measure of this study is change in self-reported effort. This measure is not assessed on natural response trials as this condition is intended to be a passive mode of observing the stimuli. Nevertheless, repeated-measures analyses of variance will again be used to evaluate the effects of stimulation on effort scores for distancing and distraction.

12. Data & Safety Monitoring: The subjects will be fully informed of the nature of the study requirements prior to enrollment and periodically throughout the study. The subject's wellbeing will be continuously monitored by the experimenter, and the Principal Investigator will report all serious adverse events in an expedited manner to the DUHS IRB office and all applicable regulatory authorities in accordance with standard operating procedures.

The study monitor will be Dr. Kevin LaBar. Dr. LaBar will ensure the quality of the study and establish that each co-investigator is complying with the investigational plan and IRB regulations. Monitoring of this protocol is simplified by the fact that this study involves a small number of investigators.

Throughout the investigation, the monitor will ensure that the facilities being used continue to be acceptable for the purposes of the study; that the investigational plan is being followed; that any changes to the protocol have received IRB approval; that accurate, complete, and current records are maintained; and that accurate, complete, and timely reports are made to the IRB. This will be accomplished through quarterly meetings during which the status of the protocol, investigators, and IRB compliance are reviewed. The monitor will review each research chart for completeness and accuracy. He will confirm that inclusion and exclusion criteria have been met for each subject enrolled, and compliance with all other aspects of the investigational plan are met.

13. Privacy, Data Storage & Confidentiality: Participants' information will be de-identified. Codes will be used in reference to participants' data. Basic demographic information will be collected but kept separate from the participant's data files. Some protected health information will be collected from the subject as means of screening the subject for eligibility in the study. All written information will be kept in locked cabinets within Duke University. All digital information will be kept in a secure Duke University server, accessible only to members of the lab or other personnel involved with the study. Analyses are typically conducted on group averages and personal information pertaining to individual subjects will never be mentioned. The de-identified data may be uploaded to a shared data repository, but will not be uploaded with any key for the general public to link participants' information to their data. The results of the studies will be disseminated in peer-reviewed academic journals. All data we keep will be de-identified, indefinitely. Subject's SSN will only be stored on paper for the interim period between getting paid for their participation in the experiment and when their receipts are cleared by Duke University Financial Services. The paper SSNs will be safely destroyed and disposed upon receipt clearance notification.

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