Perelman School of Medicine
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Reducing neural perseveration through closed loop real time fMRI neurofeedback to alleviate depressive symptoms

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Study Summary

Title	Reducing neural perseveration through closed loop real time fMRI neurofeedback to alleviate depressive symptoms
Short Title	Neurofeedback to treat depression
IRB Number	849298
Protocol Number	N/A
Methodology	Double blinded group comparison study
Study Duration	5 years
Study Center(s)	Single-center
Objectives	Primary overall objective is to test closed loop real time fMRI neurofeedback that specifically targets our hypothesized attentional mechanism of depression (i.e., neural perseveration of negative states) to reduce depression severity. The primary objective in the R61 phase is to compare the time spent in the most negative state before and after real-time neurofeedback training, comparing active vs sham training. The secondary objective is to determine the lowest # of sessions necessary. The primary objective of the R33 phase in a randomized controlled trial is to compare active an sham feedback on depression outcome and to determine the relationship between changes in neural perseveration and change in depression.
Number of Subjects	R61 Phase – 60 patients with MDD expected to enroll. R33 Phase (if approved) – 80 patients with MDD expected to enroll.

Main Inclusion and Exclusion Criteria	Inclusion: • gender, inclusive • adult aged 18 – 65 • meets Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria for MDD according to the Clinician-Administered MDD Scale for DSM-5 (unipolar depression or bipolar II depressed) • scores at least a minimum score of 16 on Montgomery Asberg Depression Rating Scale (MADRS) • normal cognition • participants must be able to read and understand English • participants must be able to provide consent Exclusion: • pregnancy (female participants) • outside age range • MRI contraindications (medical implant, claustrophobia, etc.) • use of psychoactive medication (including antidepressants) or currently in therapy • neurological disorder or any condition that in the view of the PI could impact brain data, cause depression, require medication that could cause depressive symptoms, or otherwise result in participant being unfit for study (for example, co-morbid psychotic disorders, neurological disorders, developmentally or cognitively disabled/impaired, active alcohol or drug abuse/dependence within the past 6 months) • non-English speaking • non-correctable vision loss • refusal to provide informed consent • representing an active suicide risk
Intervention	Behavioral intervention (neurofeedback)
Statistical Methodology	Linear mixed effects regression modeling will be used to assess changes in neural perseveration and MADRS over time in the active neurofeedback group. Multiple linear regression will be used to assess the relationship between reduced neural perseveration and reduced MADRS scores. Two-sample t-tests will assess group differences in task performance and symptoms after each session of treatment in order to determine the necessary dose of neurofeedback for reducing neural perseveration.

Data and Safety Monitoring Plan	We have elected to utilize a Data and Safety Monitoring Board as part of our data and safety monitoring plan.

Background and Study Rationale

This study will be conducted in full accordance with all applicable University of Pennsylvania Research Policies and Procedures and all applicable Federal and state laws and regulations.

1 Introduction

Depressed individuals process negative stimuli differently from healthy participants, leading to differences in attention, memory, and cognitive control (Mogg and Bradley 2005, Mogg, Field et al. 2005, Gotlib and Joormann 2010, Sanchez, Vazquez et al. 2013, Snyder 2013, Jones and Sharpe 2017, Koster 2017). Depressed participants also tend to show larger and more prolonged neural responses to negative stimuli (Disner, Beevers et al. 2011). Relatedly, other studies have found that depressed individuals specifically have difficulty in disengaging from negative stimuli (Armstrong and Olatunji 2012, Sanchez, Vazquez et al. 2013, Mennen, Norman et al. 2019). This inability to transition out of negative states may manifest clinically as rumination--the automatic, perseverative replay of negative thoughts (Gotlib 1982, Nolen-Hoeksema, Wisco et al. 2008).

Behavioral training has been the main approach to reduce attentional biases in depression, yet behavioral measures such as button presses and eye movements are downstream effects of underlying neural differences. Neural feedback, such as from functional magnetic resonance imaging (fMRI), allows for measures that are "closer to the source" of the biases, and thus have the potential to be more sensitive and informative. Indeed, depressed participants can show enhanced neural processing of negative stimuli that are presented quickly even in the absence of any indication from behavior (Fales, Barch et al. 2008, Suslow, Konrad et al. 2010, Victor, Furey et al. 2010). We therefore seek to combine the advantages of adaptive feedback with the potentially enhanced sensitivity of neural measurements of attention.

1.1 Background and Relevant Literature

Depression is one of the most prevalent, chronic and debilitating illnesses; it affects 10% of individuals within the past 12 months (Hasin, Sarvet et al. 2018) and is the leading cause of disability world-wide (Kessler, Aguilar-Gaxiola et al. 2009, Collins, Patel et al. 2011). Effective pharmacotherapies are available but produce responses in only approximately half of patients ((APA 2013); STAR-D) and following nonefficacy with an initial SSRI, only about 20% remit (Rush, South et al. 2020). Thus, finding additional treatment strategies to achieve better treatment outcome is highly desirable.

In this R61/R33 proposal we will test the efficacy of a new psychotherapeutic strategy, closed loop real time fMRI neurofeedback, in reducing negative attention bias and depressive symptoms. This is the first real time feedback therapy to use the person's brain state (based on all of the person's brain signal) for cloud based machine learning decoding and feedback rather than the more typical approach of conveying feedback through a separate gauge or scale. It is well established that depressed individuals have accentuated processing of negative stimuli, leading to differences in attention, memory, and cognitive control (M1-5) and more prolonged neural responses to negative stimuli (6), manifesting clinically as rumination (M1, 7). Neural feedback from functional magnetic resonance imaging (fMRI), provides measures that are "close to the source" of the biases, with the potential to be sensitive and informative. In a pilot study (Mennen et al, BP 20) we adapted a closed loop procedure and showed feasibility data for reducing neural measures of negative attention bias that was correlated with reductions in depressive symptoms.

Thus, this project will establish real-time fMRI neurofeedback as a means of reducing attention to negative stimuli by reducing neural perseveration of negative states as a treatment for MDD. Results from this line of research will inform feedback strategies and improve understanding of neural mechanisms underlying negative attention and MDD.

2 Study Objectives

2.1 Primary Objective

The overall objective of this R61/R33 is to test whether closed loop real time fMRI neurofeedback that specifically targets our hypothesized attentional mechanism of depression (i.e., neural perseveration of negative states) reduces depression severity. This study will be the first dose-finding test of real-time fMRI effect on negative attention bias.

2.2 Secondary Objectives (if applicable)

Phase R61:

- Aim 1: Target Engagement. Response to real-time vs sham neurofeedback will be determined by pre-post change in selective attention to negative stimuli.
- Aim 2: Determine the lowest "dose" of training necessary to reduce selective attention to negative stimuli.
- Exploratory Aim: Examine behavioral perseveration on negative stimuli.

Phase R33 will be conducted only if Phase R61 is successful:

- Aim 1: Conduct a randomized controlled trial (RCT) to compare the effect of real-time neurofeedback vs. sham on depression outcome in patients with MDD.
- Aim 2: Determine the relationship between the markers of neural perseveration established in the R61 phase and the reduction in depressive symptoms.
- Aim 3: Determine the durability of the treatment effect.

3 Investigational Plan

Following ascertainment of inclusion and exclusion criteria and consent, participants will be enrolled and randomized to either the active or sham group. In subsequent daily visits, they will perform the gaze task and receive neurofeedback training. In general, it is expected that the visits will occur on sequential days, except for weekends, but there will be flexibility for patient schedule. Participants will also complete 2 follow-ups. See below for visit breakdown.

- R61 phase will include:
    - 1 pre-training session (includes screening)
    - 4 training sessions (the first session includes a baseline MRI scan)
    - 1 post-training session
    - 2 follow-up sessions
- R33 phase will include:
    - 1 pre-training session (includes screening)
    - training sessions (number of sessions will be determined in the R61 phase)
    - 1 post-training session
    - 2 follow-up sessions

3.1 General Design

This study uses neurofeedback to target neural mechanisms underlying attentional bias in participants with major depressive discover (MDD), with the goal of evaluating whether this intervention can be used to reduce the negative attentional bias.

Following random assignment, participants will begin the protocol with either active neurofeedback or sham (yoked) neurofeedback.

3.2 Allocation to Interventional Group

Participants will be randomly assigned to treatment with active neurofeedback or sham. At the end of the initial assessment, a computer-generated random number list will be used to allocate participants to the two treatment conditions.

3.3 Study Measures

Sources of data includes fMRI data from MRI scanner, clinical evaluations (diagnoses, observer ratings), and behavioral gaze data.

In the R61 phase we will compare cloud based real time fMRI feedback with placebo (sham feedback) in reducing negative attention bias and depressive symptoms. This study will be the first dose-finding test of real-time fMRI effect on negative attention bias. Measures include:

- Structured Clinical Interview for DSM-5 (SCID)
    - Clinician-administered diagnostic exam
    - Completed during pre-training session for screening and eligibility assessment
- Montgomery Asberg Depression Rating Scale (MADRS)
    - Clinician-administered scale used to assess the severity of depression

    - Obtained during pre-treatment session (for screening and eligibility assessment), 3 training sessions, post-training session, and 2 follow-up sessions
- State-Trait Anxiety Inventory (STAI)
    - Self-report questionnaire used to measure types of anxiety
    - Obtained during pre-treatment session, 3 training sessions, post-training session, and 2 follow-up sessions
- Mood and Anxiety Symptom Questionnaire (MASQ)
    - Self-report questionnaire used to measure mood symptoms
    - Obtained during pre-treatment session, 3 training sessions, post-training session, and 2 follow-up sessions
- Negative perseveration during a go/no-go task
    - Go/no-go task with overlaid face/scene stimuli; brain response triggers next stimulus
    - Obtained in 3 training sessions and post-training session
- Negative gaze
    - Negative gaze collected in gaze data following each real time fMRI feedback session
    - Obtained during 3 training sessions and post-training session

In the R33 phase we will compare the effect of real-time neurofeedback vs. sham on depression outcome in patients with MDD. The number of training sessions will be determined in the R61 phase.

- Structured Clinical Interview for DSM-5 (SCID)
    - Clinician-administered diagnostic exam
    - Completed during pre-training session for screening and eligibility assessment
- Montgomery Asberg Depression Rating Scale (MADRS)
    - Clinician-administered scale used to assess the severity of depression
    - Obtained during pre-treatment session (for screening and eligibility assessment), 3 training sessions, post-training session, and 2 follow-up sessions
- State-Trait Anxiety Inventory (STAI)
    - Self-report questionnaire used to measure types of anxiety
    - Obtained during pre-treatment session, 3 training sessions, post-training session, and 2 follow-up sessions
- Mood and Anxiety Symptom Questionnaire (MASQ)
    - Self-report questionnaire used to measure mood symptoms
    - Obtained during pre-treatment session, 3 training sessions, post-training session, and 2 follow-up sessions
- Negative perseveration during a go/no-go task
    - Go/no-go task with overlaid face/scene stimuli; brain response triggers next stimulus
    - Obtained in training sessions and post-training session, although exact number will be determined in R61 phase

3.4 Study Endpoints

3.4.1 Primary Study Endpoint

Our primary aim to test the efficacy of the closed loop real time fMRI neurofeedback: does this neurofeedback that specifically targets our hypothesized attentional mechanism of depression (i.e., neural perseveration of negative states) lead to reduced depression severity? The primary endpoint would then be a change in negative attention bias following training visits. Phase R61 will focus on this negative attention bias, and Phase R33 will focus on change in depressive symptom severity.

3.4.2 Secondary Study Endpoints

Phase R61:

- Aim 1: Target Engagement. Response to real-time vs sham neurofeedback will be determined by pre-post change in selective attention to negative stimuli. Following behavioral and symptom assessment participants will receive 3 training sessions conducted in the fMRI scanner, during which participants will view overlaid neutral scenes and negative faces while attending to the scenes. Multivariate pattern analysis will quantify attention to the scenes vs. faces in real-time using a cloud-based framework that adjusts each subsequent image to reward or punish based on attention to the current image. Feedback will be delivered by changing the opacity of the images of the scene target vs face distractor. We have identified a potential neural locus of the negative attentional bias — the inability of MDD to escape from a brain state in which they are attending to negative face distractors even though task irrelevant, what we refer to as "neural perseveration" (higher conditional probability of staying in the same negative state vs. healthy individuals).
- Exploratory aim: Behavioral perseveration on negative stimuli. In addition to a neural target we will also explore a behavioral perseveration target using a gaze task (R61 Exploratory Aim). In that task, patients view a screen with positive, neutral and negative images. Using an eye-tracker, the amount of time that participants spend looking at negative stimuli after first fixating on those stimuli will be recorded and compared. To further support the hypothesis that understanding negative perseveration is relevant to brain mechanisms in depression, we will measure the same probability at the end of each day of neurofeedback treatment. The progressive change over time will provide further comparisons in the active vs sham groups.
- Aim 2: Determine the lowest "dose" of training necessary to reduce selective attention to negative stimuli. Neural and behavioral markers obtained after each session will be used to determine the lowest number of sessions that produce a significant effect, which will be chosen for the R33 phase.

R33 Phase:

- Aim 1: To conduct a randomized controlled trial (RCT) to compare the effect of real-time neurofeedback vs. sham on depression outcome in patients with MDD.
- Aim 2: To determine the relationship between the markers of neural perseveration established in the R61 phase and the reduction in depressive symptoms. Neural

perseveration on negative distractors and behavioral looking at negative stimuli will be correlated with MADRS scores.

- Aim 3: To determine the durability of the treatment effect.

4 Study Population and Duration of Participation

4.1 Duration of Study Participation

Following consent and ascertainment of inclusion and exclusion criteria during pre-training session, participants will be enrolled and randomized to either the active or sham group. In subsequent daily visits, they will perform the gaze task and receive neurofeedback training. In general, it is expected that the visits will occur on sequential days, except for weekends, but there will be flexibility for patient schedule. Participants will also complete a follow-up at 1 month. The patients will follow the treatment course as best as possible, however, the protocol does allow for flexibility contingent on patient availability, MRI availability, and other scheduling factors.

As a result, total duration is expected to be approximately 6 weeks, with some room for flexibility in scheduling. A schedule of visits for Phase R66 is included below:

Visit	Pre NF	NF 1	NF 2	NF 3	Post NF	1 Month
Inclusion/Exclusion	SCID-5	-	-	-	-	-
Depression Severity	MADRS	MADRS	MADRS	MADRS	MADRS	MADRS
Mood Symptom Self Report	STAI & MASQ	STAI & MASQ	STAI & MASQ	STAI & MASQ	STAI & MASQ	STAI & MASQ
MRI Acquisition	-	Structural	-	-	-	-
	-	Go/no-go	Go/no-go	Go/no-go	-	-
Behavioral Assessment	Gaze	Gaze	Gaze	Gaze	-	-

4.2 Total Number of Subjects and Sites

Enrollment and administrative site will be at the University of Pennsylvania.

R61 Phase will enroll 60 patients with MDD, and R33 Phase will enroll 80 patients with MDD. To account for attrition 60 participants will be enrolled in R61 Phase with 54 anticipated to complete full data collection (27 in each arm). To account for attrition 80 participants will be enrolled in R33 Phase with 72 anticipated to complete full data collection (36 in each arm).

4.3 Inclusion Criteria

- gender, inclusive
- adult aged 18 – 65

- meets Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria for MDD according to the Clinician-Administered MDD Scale for DSM-5 (unipolar depression or bipolar II depressed)
- scores at least a minimum score of 16 on Montgomery Asberg Depression Rating Scale (MADRS)
- normal cognition
- participants must be able to read and understand English
- participants must be able to provide consent

4.4 Exclusion Criteria

- pregnancy (female participants)
- outside age range
- MRI contraindications (medical implant, claustrophobia, etc.)
- use of psychoactive medication (including antidepressants) or currently in therapy
- neurological disorder or any condition that in the view of the PI could impact brain data, cause depression, require medication that could cause depressive symptoms, or otherwise result in participant being unfit for study (for example, co-morbid psychotic, neurological disorders, developmentally or cognitively disabled/impaired, active alcohol or drug abuse/dependence within the past 6 months).
- non-English speaking
- non-correctable vision loss
- refusal to provide informed consent
- representing an active suicide risk

4.5 Subject Recruitment

All participants will be recruited through the University of Pennsylvania and surrounding community. For both phases, recruitment will occur through the Center for Neuromodulation is Depression and Stress (CNDS) directed by the PI. All subjects will express interest by initiating contact with the research staff for a center wide phone screening or self-screening procedure. All subjects fitting inclusion criteria will be approached by study staff to continue in the study. This study will also be advertised on online sources such as Facebook. Study coordinators in the present study will use the results in REDCap as a source of recruitment, at which point those subjects will undergo the full phone-screen. This phone screen will also be collected and stored in REDCap. In addition to recruiting from the CNDS, we will recruit from the larger Philadelphia community through targeted advertisements and referral streams at the University of Philadelphia. This includes both print and online sources. All recruitment materials, including but not limited to flyers, brochures, referral letters, online postings, and email templates will be IRB-approved before distribution of any of these material.

4.6 Vulnerable Populations: N/A

Children, pregnant women, fetuses, neonates, or prisoners are not included in this research study.

5 Study Procedures

In the R61 phase we will compare cloud based real time fMRI feedback with placebo (sham feedback) in reducing negative attention bias and depressive symptoms. This study will be the first dose-finding test of real-time fMRI effect on negative attention bias.

In the R33 phase, if approved in future, we will compare the effect of real-time neurofeedback vs. sham on depression outcome in patients with MDD. The number of training sessions will be determined in the R61 phase.

Sources of data includes fMRI data from MRI scanner, clinical evaluations (SCID, MADRS), self-report questionnaires (STAI & MASQ), and behavioral gaze data (behavioral assessment from go/no-go task). Below is a table that outlines what assessments and procedures will be completed at each visit:

Procedure	Pre-training Session (Screening Visit)	Training Session 1	Training sessions (2-3)	Post-training session	Follow-up Session
Clinical Assessments	X (SCID & MADRS)	X (MADRS)	X (MADRS)	X (MADRS)	X (MADRS)
Self-report Questionnaires	X	X	X	X	X
Medication History	X				
Demographics Survey	X				
MRI Scan		X (baseline)	X		
Behavioral Task	X	X	X		

During the initial week, there will be one initial pre-training/screening visit (approx. 3-4 hours), 3 training visits (approx. 4-5 hours each), and one post-training visit (approx. 1 hour). Within 3 months, there are 2 follow-up sessions after the treatment is over (approx. 1 hour each).

Does your study use MRI? (CAMRIS is the appropriate contact for all studies involving MRIs)

☒ Yes ☐ No (If No, no CAMRIS review needed)

Check of all that apply:

☐ 1.5T MRI
☒ 3T MRI
☐ 7TMRI

Does the MRI use investigational sequences and/ or coils?
(See Experimental Device Clause)

☐ Yes ☒ No ☐ Unsure (if unsure be sure to contact

CAMRIS)

Does your study include pregnant women?

(See Pregnancy Clause and Justification)

☐ Yes ☒ No

Does the MRI require the use of Contrast Agents?
(See Contrast Risks)

☐ Yes ☒ No

Does your study involve the exposure to radiation, radiotracers and/or radiological imaging modalities?

☐ Yes ☒ No (If No, no RRSC review is needed)

Will any of the radiation exposure result from procedures that are or could be performed solely as a result of a subject's participation in the research protocol?

☐ Yes ☒ No

The following are examples of procedures involving ionizing radiation:
(Review appendix 15.3 and appendix 15.5)

- X-rays (examples: CT scan, chest x-ray, hand/wrist x-ray, abdomen x-ray, DEXA, pQCT, Fluoroscopy/Angiography)
- Nuclear Medicine scans (examples: FDG-PET, PET/CT, Tc-99m, SPECT, MUGA, bone scan)
- If you are unsure please contact Will Davidson in EHRS (wed@ehrs.upenn.edu).

Ultrasound

☐ Yes ☒ No

If yes, there is no protocol specific language to include but please contact Susan Schultz at: susan.schultz@uphs.upenn.edu

Will your study be using CT Scans? (CACTIS is the appropriate contact for studies involving CT scans)

☐ Yes ☒ No

Studies involving Nuclear Medicine: Will subjects be undergoing any of the following procedures specific to research:

☐ MUGA
(See Nuclear Medicine-Muga Scan)
☐ PET/CT Scan
(See PET/CT Scan)
☐ Bone /DXA
(See Bone Scan)

Check off all of the following procedures that will be performed in your research- each option you select will link to the template language document:

☐ Apheresis/plasma exchange

- ☐ Leukapheresis
- ☐ Bone Marrow Biopsy or Aspirate
- ☐ Use of AP clinical specimens
- ☐ Biopsies- check those which apply
- ☐ Blood draw

5.1 Pre-Training Visit

The pre-training visit will include screening procedures.

Participants will be recruited, consented, and evaluated. They will also complete MRI safety screening forms and self-report medical history. This includes completing informed consent. Each patient's medical history is reviewed by Dr. Sheline and, when clinically indicated, a physical examination and appropriate laboratory tests will be obtained to ensure that patients are diagnostically eligible. Consenting patients will be diagnosed with the Structured Clinical Interview for DSM-5. Participants who meet eligibility requirements will be screened using the MADRS, which will be the primary outcome measure and will have a minimum score of 16. Participants will also complete the STAI & MASQ.

In addition to a neural target we will also explore a behavioral perseveration target using a gaze task. In that task, patients view a screen with positive, neutral and negative images. Using an eye-tracker, the amount of time that participants spend looking at negative stimuli after first fixating on those stimuli will be recorded and compared. To further support the hypothesis that understanding negative perseveration is relevant to brain mechanisms in depression, we will measure the same probability at the end of each day of neurofeedback treatment. The progressive change over time will provide further comparisons in the active vs sham groups.

5.2 Study Intervention or Observational Phase (Give this section a name that is relevant tothe design of your study)

5.2.1 Training Visit 1

Following ascertainment of inclusion and exclusion criteria and consent, participants will be enrolled and randomized to either the active or sham group. The active training group will receive baseline structural and functional MRI scans, which will function as the baseline MRI scans. Participants will also perform the behavioral gaze task and complete a MADRS, STAI, and MASQ.

5.2.2 Training Visits 2-3

In subsequent daily visits, they will perform the gaze task and receive neurofeedback training. Participants will also complete a MADRS, STAI, and MASQ.

5.2.3 Post-training Visit

During the post-neurofeedback training session, participants will complete only a MADRS, STAI, and MASQ.

5.2.4 Follow-up Visits 1-2

Participants will also complete 1 follow-up visit: at one month from the post treatment visit, participants will complete a MADRS, STAI, and MASQ during these follow-up visits.

5.2.5 End of Study Visit

N/A

5.3 Unscheduled Visits

Unscheduled visits will be handled only if deemed necessary by study staff, for instance a participant presented to the ER during study participation, study staff may request the patient come in between visits for evaluation.

5.4 Subject Withdrawal

Participants may be withdrawn from the study by staff if deemed necessary for their health or safety or if participants have not been following instructions. We anticipate that some participants may withdraw. We do not expect early termination of participation due to patient or investigator withdrawal to have any impact on safety or well-being of participants.

5.4.1 Data Collection and Follow-up for Withdrawn Subjects

N/A

5.5 Early Termination Visits

If deemed necessary to terminate a patient's participation in the study, they will be contacted by study staff to communicate this and the reason why. No other information will be collected from the terminated participant. Participant will complete end-of-study procedures as needed (receiving compensation, etc.).

5.6 Efficacy Evaluations (only if applicable)

Montgomery Asberg Depression Rating Scale (MADRS) will be used to examine efficacy of study intervention.

5.7 Pharmacokinetic Evaluation (only if applicable): N/A

5.8 Genetic Testing (only if applicable): N/A

5.9 Safety Evaluation (only if applicable)

The primary investigator will routinely monitor and evaluate study procedures for potential increased risk.

6 Statistical Plan

6.1 Sample Size and Power Determination

R61 Phase: A total of 60 (n=30 active neurofeedback, n=30 sham feedback) will be enrolled. Allowing for a 10% loss of subjects, based on our preliminary data, the sample size (i.e. at least 27 patients per arm with valid post-treatment data) was chosen so that the study would have adequate power to detect between-group differences of moderate to large between group effect sizes (see power analysis below).

- For a one-sample t-test with a two-sided alternative and type I error rate of 5%, 27 participants will yield 80% power for a Cohen's $d = 0.56$. This is sufficient power to detect the effect size of $d = 0.83$ for reduction in neural perseveration found in the pilot study. For a two-sample t-test with two-sided alternative and type I error rate of 5%, 27 participants per arm will yield 80% power for a Cohen's $d = 0.86$ or larger. The statistical analysis for power determination and sample size is subject to change as data is collected over the course of the study.

R33 Phase: A total of 80 participants with MDD (n=40 real time neurofeedback, n=40 sham feedback) will be enrolled as above in a randomized controlled clinical trial. Allowing for a 10% loss of subjects, based on our preliminary data, the sample size (i.e. at least 36 patients per arm with valid post-treatment data) was chosen so that the study would have adequate power to detect between-group differences of moderate to large between group effect sizes (see power analysis below).

- For a one-sample t-test with a two-sided alternative and type I error rate of 5%, 36 participants per arm will yield 80% power for a Cohens d = 0.53 or larger, which is sufficient to detect the effect size of 0.93 Visit 1 to post-treatment MADRS score decrease in the pilot data (**Hypothesis 1**). For a two-sample t-test with a two-sided alternative and type I error rate of 5%, 36 participants will yield 80% power for a Cohens $d = 0.74$ or larger. **Hypothesis 2** will utilize Pearson correlation between change in MADRS and change in negative attention scores. If nonlinearity is detected, we will employ a Spearman correlation analysis. A sample size of n=36 corresponds to 80% power to detect a significant (at 5% alpha level) correlation as low as r=0.45, which is sufficient to detect the effect size of r=0.48 found in the pilot data (**Figure 1**). **Hypothesis 3** will use a two-sample t-test comparing real vs sham NF. Pilot study data indicated a change in MADRS from baseline to 3 month follow-up corresponding to Cohen's d=0.95. A two-sample t-test, with 36 per group, at 5% significance level, gives 80% power to detect d=0.74 or larger.

6.2 Statistical Methods

Statistical analysis will be performed using the R statistical environment assuming 5% type I error rates. Linear mixed effects regression modeling (using the lme4 R package) will be used to assess evidence of reduced neural perseveration and reduced MADRS over time in the active neurofeedback group. Two-sample t-tests will be used to compare differences in neural perseveration and MADRS scores between the active neurofeedback and sham (yoked) neurofeedback groups after each additional session of treatment in order to establish the lowest dose of training necessary to significantly reduce neural perseveration. We will utilize multiple linear regression to assess the relationship between reduced perseveration and the reduction of MADRS scores in the active neurofeedback group while accounting for various confounds.

6.3 Control of Bias and Confounding (if applicable, typically observational study or if randomization is not taking place)

6.3.1 Baseline Data

Participants will be matched on demographic data.

6.3.2 Analysis of Primary Outcome of Interest

We will use a two-sample t-test comparison of active neurofeedback vs sham to determine the effect on MADRS scores.

6.3.3 Pharmacokinetic Analysis (only if applicable): N/A

6.3.4 Interim Analysis (only if applicable): N/A

7 Safety and Adverse Events

7.1 Definitions

7.1.1 Adverse Event

An adverse event (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

7.1.2 Serious Adverse Event

Serious Adverse Event

Adverse events are classified as serious or non-serious. A serious adverse event is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- required intervention to prevent permanent impairment or damage
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as non-serious adverse events.

For additional information on definitions and clarifications which may be helpful in creating the safety monitoring portion refer to appendix 15.7

7.2 Recording of Adverse Events

At each contact with the subject, the investigator will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period will be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study intervention or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study intervention or study participation will be recorded and reported immediately.

7.3 Relationship of AE to Study

The relationship of each adverse event to the study procedures will be determined by the PI and co-PI and relationships will be classified as either: definitely related, probably related, possibly related, unlikely or unrelated.

7.4 Reporting of Adverse Events and Unanticipated Problems

Unexpected and related Adverse Events will be reported to the IRB by study staff within 72 hours of knowledge of the event; all other adverse events will be reported at the time of continuing review. Reporting of Serious Adverse Events will occur within 24 hours of knowledge of the event.

7.4.1 Follow-up Report

If an SAE has not resolved at the time of the initial report, follow-up reports with all relevant new, or reassessed, information will be submitted to the IRB until the SAE resolves or stabilizes.

7.4.2 Investigator reporting: notifying the study sponsor (if applicable)

N/A

7.4.3 Data and Safety Monitoring Plan

7.4.3.1 Data Safety Monitoring Board (if applicable)

Because study subjects will be receiving a device-based intervention as part of this study protocol, we have elected to utilize a Data and Safety Monitoring Board as part of our data and safety monitoring plan. The frequency of Penn DSMB review for this protocol will be once every 12 months based on IRB recommendations consistent with the assessed risk status of the study.

Dr. Sheline will convene a Data and Safety Monitoring Board (DSMB). The DSMB will include a biostatistician with expertise in randomized clinical trial methodology, a researcher with expertise in neuroimaging, and a clinical psychologist or psychiatrist. The members of the DSMB will not be involved in this project and will not be collaborators on any other of the investigators' projects nor in their employ. DSMB members will provide the PI (and NIH, as required) with qualifications and a statement indicating that they have no direct involvement with the study or any conflicts of interest with the investigators or institutions conducting the study. They will meet annually to 1) monitor the safety, quality and conduct of this study and 2) decide whether adequate subject safeguards are in place. The DSMB will review: 1) the progress of the proposed study, including assessments of data quality and participant recruitment, accrual and retention; 2) outcome and adverse event data to determine whether there is any change to the anticipated benefit-to-risk ratio of study participation and whether the study should continue, be changed, or terminated; 3) external factors or relevant information (e.g., pertinent scientific literature reports or therapeutic developments, results of related studies) that may have an impact on the safety of study participants or the ethics of the research study; and 4) study procedures designed to protect the privacy of the research subjects and the confidentiality of their research data. The study statistician will be responsible for generating a de-identified annual report of key events that will be reviewed as part of the safety monitoring of the protocol. The tentative list of key events will include and more specifically indicate: 1) side effects to the study treatment, 2) hospitalization, and 3) premature drop-out from treatment. The key events will be reviewed at

the first meeting of the DSMB to obtain the DSMB members' input into the list and to add any other events or measures that they feel would be relevant to include for evaluating the safety and conduct of the clinical trial. Prior to each DSMB meeting, the data manager/research coordinators will prepare a report to be reviewed during that meeting. The report will include the number of participants who signed consent for the study and were randomized, the number of post-randomization dropouts, reasons for these dropouts, and any safety concerns, adverse events, etc. An up-to-date consent form will be provided, as well as a summary of measures taken to protect confidentiality (e.g. data storage, use of coded ID numbers, etc). The PI will also prepare a report summarizing any new data/evidence that might alter the risk/benefit ratio for participating in the study (e.g., newly published studies, etc.). Data will be presented to the DSMB in such a way as to maintain patient confidentiality. Based on the information provided to the Penn DSMB, once every 12 months the DSMB will issue a report that summarizes the following: All serious and unexpected adverse events or other unanticipated problems that involve risk to study participants, and whether these appear related to the study based interventions or research assessment protocols. Reports will not disclose the treatment arm of the study for relevant subjects unless this disclosure is required for safety reasons. Note that any serious adverse event (SAE) will be reported to the Penn IRB within 24 hours according to standard regulations. The IRB defines a serious adverse event as: "any adverse experiences occurring that result in any of the following outcomes: death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. For the purposes of this policy, death is never expected." The PI will take responsibility for reporting any serious and unexpected adverse events in a timely fashion directly to the Penn DSMB. The PI will also report serious and unexpected adverse events or other unanticipated study problems or variances to the Penn IRB. Actions taken by the IRB in response to adverse event reports will be immediately reported to the Penn DSMB. Statistical analysis of adverse event data will be provided by Dr.Shinohara, the study Biostatistician.

8 Study Administration, Data Handling and Record Keeping

8.1 Confidentiality

We will collect the following PHI: name, address, social security number (for compensation purposes) visit dates, telephone number, and email address. Patients entering the study will be given a unique identifying code. This code will be used on all data obtained from scans or study visits. Only one password protected document connecting the code with the participant name (in the form of first two letters of the first name, first three letters of the last name) will exist. Everything will be immediately coded and this coded information will be stored in secure cabinets inside locked rooms or in password protected, IRB compliant online databases, such as REDCap. PHI will be stored separately in secure cabinets inside locked rooms. Coded data will be stored on a secure server at the University of Pennsylvania through the Neuroscience Neuroimaging Group computing cluster. MRI data are securely copied on the uphs network directly from the MRI machine at Stellar Chance to this computing cluster without separate physical storage. Coded data are directly uploaded to the computing cluster from the computers on which the data are collected. The Penn computers are in our secured lab space and connected directly to the uphs encrypted network. None of these data will contain personal identifiers such

as name, social security number, address, or phone number. At the conclusion of the study, coded copies of the data may be maintained at the University of Pennsylvania in its de-identified form for future analyses. Computer-based files containing electronic PHI, that are not part of the EMR, will be kept on the Penn Network server.

The PI will directly train the study staff in issues of maintaining data integrity and confidentiality and will stress the critical importance of subject confidentiality in training of all project staff and will keep reiterating this point as opportunities arise in handling of such material. All data collection and storage will use the following safeguards to protect data integrity and subject confidentiality: (1) All members of the project will receive human subjects training and certification through the Collaborative Institutional Training Initiative (CITI) curriculum; (2) all staff will undergo the necessary required trainings; and (3) all project staff will maintain up-to-date certification on research subject confidentiality and privacy. Data from interviews and questionnaires will be collected by members of the clinical assessment team. The research staff will be responsible for immediate transfer of the data to the secure storage area, and for entering the data to secure online databases. All data will be identified and labeled only by subject ID numbers and will be stored separately from the identifying information and from consent and assessment forms. This study will utilize the secure, web-based Research Electronic Data Capture (REDCap) system for data input. Imaging data will be de-identified and stored on secure servers. Access to password-protected databases will be limited to the investigators and trained staff. Paper forms and data will be stored securely within the lab of Dr. Sheline. Data access will be limited to the Investigators and study staff who will receive human subjects training and certification through the CITI curriculum. Any staff member who has access to subjects or data will sign a confidentiality agreement before handling data and will receive training in the critical importance of subject confidentiality. Every effort, and ongoing adjustments, will be made to ensure that the identity of subjects cannot be determined by the use of the data. Future use of the data includes research, demonstration, publication, public performance and archiving. Subjects' permission for further use of their data, in de-identified form, will be obtained via consent. Data will be presented in aggregate form with identifiers removed.

8.2 Data Collection and Management

Data from interviews and questionnaires will be collected by members of the clinical assessment team. The research staff will be responsible for immediate transfer of the data to the secure storage area, and for entering the data to secure online databases. All data will be identified and labeled only by subject ID numbers and will be stored separately from the identifying information and from consent and assessment forms. This study will utilize the secure, web-based Research Electronic Data Capture (REDCap) system for data input. Imaging data will be de-identified and stored on secure servers, as clarified below. Access to password-protected databases will be limited to the investigators and trained staff. Paper forms and data will be stored securely within the lab of Dr. Sheline. Data access will be limited to the Investigators and study staff who will receive human subjects training and certification through the CITI curriculum. Any staff memberwho has access to subjects or data will sign a confidentiality agreement before handling data andwill receive training in the critical importance of subject confidentiality.

Additionally, our analysis pipeline will send scan data to cloud computing resources via an SSL

connection provided by the UPHS IT Group hosted in their Microsoft Azure environment. All metadata fields containing PHI will be removed prior to sending the scan data to the cloud. UPHS IT uses an Azure ExpressRoute, which is a private, dedicated connection, to extend on-premises networks into the cloud while following Penn Medicine policies and standards for data management and security within a hybrid environment. This in part rests upon HIPAA compliance through our existing BAA with Microsoft. Azure has enabled the physical, technical, and administrative safeguards required by HIPAA and the HITECH Act inside the in-scope Azure services. In this way, cloud and on-premises resources will be on secure and isolated networks and require the same security credentials and Role Based Access Controls (RBAC). The data will be transmitted over the ExpressRoute for processing in the cloud and may be temporarily stored on encrypted disk in the Azure based compute resource. In this way the movement of data from the on-premises computer in the scanner to the UPHS Azure compute resource will never leave the UPHS hybrid network environment. At the conclusion of the study, coded copies of the data may be maintained at the University of Pennsylvania in its de-identified form for future analyses. Computer-based files containing electronic PHI, that are not part of the EMR, will be kept on the Penn Network server.

8.3 Records Retention

Future use of the data includes research, demonstration, publication, public performance, and archiving. Subjects' permission for further use of their data, in de-identified form, will be obtained via consent.

9 Study Monitoring, Auditing, and Inspecting

9.1 Study Monitoring Plan

The PI will be responsible for overarching project operations and ensuring the integrity of the research procedures. These responsibilities include: ensuring that adequate safety protocols are developed and implemented, overseeing data management and data analysis, and communicating with the University of Pennsylvania Institutional Review Board (UPenn IRB). Dr. Sheline will also oversee and be responsible for procedural integrity and the safety of subjects. Prior to initiation of this study, the study protocol will be submitted for review and approval to the UPenn IRB.

Dr. Sheline will assume responsibility for statistical design and analysis of the study data in collaboration with Co-I's named to this project. Overseen by the PI, monitoring of data will be ongoing throughout the project. Specifically, the clinical assessment team will collect information regarding adverse events, during the clinical visits. Any adverse events that are reported during these sessions will be documented and reported to Dr. Sheline to determine the next steps (such as referral to the emergency room for further evaluation in the case of severe adverse events or worsening suicidality). Any unexpected adverse events, unexpected problems that involve risk to the participants or others, or breaches of confidentiality, will be documented and reported immediately to the PI, who will determine the next steps (such as reporting to the IRB or NIH, as indicated). All regulatory and subject research files will undergo monitoring by the UPenn IRB. The UPenn IRB will also ensure that the study is conducted in accordance with the protocol and inclusion/exclusion criteria as approved.

9.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

10 Ethical Considerations

This study is to be conducted in accordance with applicable US government regulations and international standards of Good Clinical Practice, and applicable institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study.

10.1 Risks

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

MRI Scan:

- **Claustrophobia**: participants may experience claustrophobia within the MRI scanner. A MRI scan requires participants lay in a partially enclosed space inside the scanner. Some people may find this to be uncomfortable and claustrophobic. Participants will be given an emergency call button in the scan and reminded to notify study staff if they suffer from claustrophobia.
- **Magnetic Fields:** There are 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 participants with protective earplugs as necessary and make every attempt to ensure their comfort with blankets, etc. during their time in the scanner.
- **Flying Objects**: The known risks associated with this study are minimal. Implanted medical devices and metallic foreign fragments inside a participant's body may pose a risk if they were to enter the MRI magnet room. Therefore, each participant will complete an MRI safety screening form at screening and prior to each scan. The greatest risk is a magnetic object flying through the air toward the magnet and hitting a participant. 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 participants are in the magnet, the door to the room will be closed so that no one inadvertently walks into the room.
- **Incidental Findings Clause**: it is possible that during the course of the research study, the research staff may notice unexpected finding(s) on a participant's images. Should this occur, the finding(s) will be considered by the appropriate personnel and the PI will inform participants if necessary for medical follow-up. These possible finding(s) will not be disclosed to the participant unless deemed necessary by the PI and reviewing radiologist in order to avoid unnecessary anxiety for participants.

- **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 possible benefit from participating in this protocol for a pregnant woman, we will exclude pregnant women.

Risk to confidentiality: As with any research, there is a rare risk that confidentiality could be breached in this study. Breaches in confidentiality could impact a participant's future insurability and/or employability. In compliance with HIPAA and GCP guidelines, we will protect participant information and PHI to the extent permitted by law with the following measures:

All study materials (with the exception of informed consent, financial, and safety forms) will only be identified with a randomly generated research identification number. All study documents with identifiable information (i.e. informed consent, financial, and safety forms) will be stored separately from the participant file in a double-locked environment. As hard copy source documents are collected, 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 identified only with a randomly generated research identification number.

For data sent to cloud computing resources, we mitigate risk by using the HIPAA compliant Azure Cloud and ExpressRoute which controls the communication path between on-premises and cloud computing resources through established secure channels, thus providing a level of isolation and Role Based Access Control as for any Penn Medicine computing system. In addition, during scan processing, we anonymize metadata fields containing PHI and use encrypted disks for any storage needed during cloud processing.

10.2 Benefits

Participants may not receive any benefits from participating in this research. However, participants may experience a decrease in depressive symptoms. Although there may be no direct benefit to participants, learning further about treating depression is valuable knowledge to be gained.

10.3 Risk Benefit Assessment

This study is minimal risk. There is essentially zero risk of harm from the research procedures (MRI, assessments of symptoms, etc.). The potential benefit to society through the increased understanding of the mechanisms of closed loop real time fMRI neurofeedback far outweighs the potential risk from the MRI procedures. Additionally, those who would be unable to tolerate an MRI scan will be screened out.

Alternatives to Participation: the alternative to participation is to not participate.

10.4 Informed Consent Process / HIPAA Authorization

Consent will be obtained by research coordinators or the PI. Consent will be obtained in a private room where the coordinator and investigator(s) can explain the purpose of the study procedures

and aims. Furthermore, they will explain that participating is completely voluntary and that not participating will not impact them negatively. The potential participant will be given the option to consider study enrollment and will not be forced to make a decision the same day. If they decide to participate, a combined consent and HIPAA form will be signed by research staff and the patient. The patient will be reminded before and after enrolling, and before any research procedure that their participation is optional and has no impact on the care they can expect.

10.4.1 Alterations to Typical Consent Process (only include if applicable): N/A

10.4.1.1 Waiver of Consent (In some cases for screening/portions of that study that qualify as minimal risk, a waiver of documentation of consent may be permissible IRB SOP)

10.4.1.2 Waiver of Written Documentation of Consent

10.4.1.3 Waiver of HIPAA Authorization

11 Study Finances

11.1 Funding Source

NIMH pending grant.

11.2 Conflict of Interest

All conflicts of interest will be disclosed, and all University of Pennsylvania Investigators will follow the University of Pennsylvania Policy on Conflicts of Interest Related to Research.

11.3 Subject Stipends or Payments

Participants will receive compensation for their time and participation, up to $500 for study completion, as the study procedures include several scans per participant and assessment time outside of the scanner: $25 for initial pre-training/screening, $50 for each training session, $25 for post-training session, and $25 for the follow-up session. Participants receive an additional $275 at the end for completing the study.

Compensation will be dispensed via Greenphire ClinCard at the end of study participation, once all study procedures are complete.

12 Publication Plan

PI will have full access to data set and will be responsible for all publications that would accrue from this study.

13 References

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14 Attachments

Consent form is attached.

15 Appendices

15.1 ***Studies Involving Research MRIs***

15.2 ***Studies Involving Research Radiation***

15.3 ***Studies Involving Research CT Scans***

15.4 ***Studies Involving Nuclear Medicine Regulated Research Procedures***

15.5 ***Research studies involving Pathology and Lab Medicine***

15.6 Reference for Safety Reporting Section- Common Definitions for Developing AdverseEvent Tracking and Serious Adverse Event Reporting Protocol

Adverse Event Reporting Period
The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any adverse event including death occurring at any time after a subject has discontinued or terminated study

participation, that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Abnormal Laboratory Values

A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- *The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality*
- *The abnormality suggests a disease and/or organ toxicity*
- *The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the study procedures, more frequent follow-up assessments, further diagnostic investigation, etc.*

Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- *Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should not be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.*
- *Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.*
- *Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.*

Penn IRB Definition of Unanticipated Problems Involving Risk to Subjects or Others

Any incident, experience, or outcome that meets all of the following criteria:

- <u>*Unexpected in nature, severity, or frequency*</u> *(i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc.)*
- <u>*Related or possibly related to participation in the research*</u> *(i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)*
- <u>*Suggests that the research places subjects or others at greater risk of harm*</u> *(including physical, psychological, economic, or social harm).*

15.8 Source Documents

N/A

15.9 Case Report Forms (CRFs)

N/A