Mass General Brigham

Institutional Review Board
Intervention/Interaction Detailed Protocol

Principal Investigator:	Dr. Paolo Cassano, MD, PhD
Project Title: Bipolar Disorder (TPEB)	Transcranial Photobiomodulation for Executive Function in
NCT Number:	NCT05408637
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1. Background and Significance

Bipolar disorder (BD) is characterized by debilitating depressive and manic or hypomanic episodes, effecting an estimated 45 million worldwide[1]. The lifetime prevalence rate is estimated at 1% for BD in general, with specific prevalence rates of 0.6% for BD type-I, 0.4% for BD type-II, and 1.4% for subthreshold BD[2]. BD is among the most impairing psychiatric disorders, typically causing pronounced deterioration in quality of life. Furthermore, BD is associated with premature mortality due to a suicide rate 10-30 times higher than the general population[3]. The economic burden of BD on society is high, ranking 12th in causing disability worldwide according to the World Health Organization[4]. People with BD are at particular risk of acting impulsively when experiencing manic symptoms, with a significant association between impulsivity and severity of manic symptoms. However, even when in a euthymic state, people with BD retain high impulsivity[5]. These high-risk, impulsive, unrestrained behaviors can lead to harmful psychological, social, and financial outcomes.

FDA-approved medications for manic symptoms, such as Lithium, Carbamazepine, Valproate, and antipsychotics, have significant drawbacks due to poor tolerability, including the risk of metabolic syndrome, cognitive dulling, sexual dysfunction, and anhedonia. Consequently, nonadherence to medications is common in BD, with a reported rate of approximately 50%[6]. This nonadherence carries a high risk of relapse, recurrence of depression, mania and psychosis, hospitalization, and suicide attempt, especially after abrupt discontinuation of medications. Overall, nonadherence decreases the likelihood of achieving remission and recovery. While medications have been shown to reduce impulsivity, with combination antipsychotics and mood stabilizers having a greater effect than mood stabilizers alone, on the whole these impulsivity scores continue to be higher than healthy controls[7].

There is promise in the use of device-based interventions to control manic symptoms. Prior to the advent of mood stabilizers and antipsychotic medications, electroconvulsive therapy (ECT) was the only −and very effective− intervention for mania, mixed states, and delirious mania[8]. Nowadays, the use of ECT for the treatment of manic symptoms is limited by poor tolerability, stigma, access, lack of specialists, cost, healthcare inequity, and national laws. ***Modern noninvasive brain stimulation (NIBs) could potentially achieve the same efficacy of ECT in controlling manic symptoms, however with better tolerability, lower stigma, and easier access.***

Impulsivity, associated with poor decision-making, is a prominent manic symptom, often associated with severe functional impairment. Furthermore, as impulsivity remains high in BD subjects outside of a manic state, it may represent a core feature or trait of BD. Recent imaging studies have shown hyperactivation of ventral striatum and ventromedial PFC when anticipating rewarding outcomes in euthymic patients[9] as well as striatal activity during anticipation being more strongly modulated by the reward value of prospects in subjects with subsyndromal hypomania[10]. Accordingly, most treatment studies show reduced impulsivity by neuromodulation of the prefrontal cortex (PFC). Specifically, high-frequency rTMS (excitation) on right dorsolateral PFC (dlPFC) decreases hasty, impulsive choices driven by immediate reward[11-14]. Therefore, it is evident that the dlPFC plays an essential role in some of the cognitive processes of impulsivity. Use of NIBs on dlPFC could reduce impulsivity in patients with bipolar disorder, depression, high

suicidality, and addictions. Similarly, bilateral, right anodal (excitation) and left cathodal tDCS on dlPFC reduces impulsivity[14]. Therefore, excitation of right dlPFC (R-dlPFC) by NIBs is a potential mechanism for treatment of manic symptoms such as impulsivity, while preserving physical health, individual functioning, and quality of life.

Mainstream NIBs devices, such as rTMS and tDCS, are limited by the complexity of their administration, which necessitates frequent in-office sessions with specialized staff. ***Mainstream NIBs are therefore not scalable to the large needs of our society. Instead, at-home, self-administered NIBs could lead to broad access to non-stigmatizing, well-tolerated interventions for manic symptoms.*** Transcranial photobiomodulation (t-PBM) with near-infrared light (NIR) over the forehead is a novel NIBs, which is inexpensive, user-friendly and can be safely administered at home without supervision[15].

A substantial body of literature proves that t-PBM with NIR penetrates deeply into the cerebral cortex, modulates cortical excitability[16,17], and improves cerebral perfusion[18-20] and oxygenation[21]. Its safety was demonstrated in 1,410 acute stroke patients[22,23]. t-PBM improves inhibition, attention, memory, working memory and learning[24-32], with evidence for cognitive benefits in both healthy individuals and in neuropsychiatric patients. ***t-PBM is ideally suited to excite R-dlPFC and to improve inhibition − similarly to rTMS and tDCS − with the substantial advantage that t-PBM is also suitable for in-home, self-administration.*** In the proposed study, we will test t-PBM on R-dlPFC to control impulsivity (improve decision making) in patients with a diagnosis of bipolar disorder and currently in the spectrum from euthymic to hypomanic. We will also use cerebral blood flow as the most reliable biomarker of target engagement of R-dlPFC.

Mechanistically, t-PBM with NIR (wavelength 800–1100 nm) is absorbed by the cytochrome C oxidase (CCO) in neuronal mitochondria, leading to an increased synthesis of adenosine triphosphate (ATP), along with photodissociation of nitric oxide (NO) and cerebral vasodilation and subsequent increase in cerebral blood flow (CBF)[33]. t-PBM increases cerebral blood flow (CBF) based on SPECT[18,34], Doppler Ultrasound[20,21], and fNIRS reports. This proposal will use the fMRI BOLD signal as the biomarker of CBF change induced by t-PBM. The BOLD signal was previously validated as a marker of target engagement and as a predictor of treatment outcome in other NIBs[35,36]. t-PBM to the R-dlPFC led to both increase of BOLD signal and to cognitive improvement in adults with cognitive deficits[37]. ***By engaging the CBF (BOLD), we will test the propensity of t-PBM to modulate R-dlPFC in patients with impulsivity due to bipolar disorder.***

At MGH, we are conducting a single-blind, sham-controlled (paired sample) study to test the effect of bilateral t-PBM on fMRI BOLD signal (dlPFC) in adults (n=15) with major depressive disorder. We have demonstrated feasibility for multiple t-PBM sessions per week and for the delivery of t-PBM within MRI scanner, while recording BOLD signal (NCT04366258). A collaboration between MGH and colleagues in Italy piloted bilateral t-PBM in adults (n=4) with BD[38]. t-PBM was helpful in alleviating BD residuals, including impulsivity and irritability.

2. Specific Aims and Objectives

1. **To test the effect of a single t-PBM session on cerebral blood flow (CBF), while irradiating R-dlPFC, in subjects with impulsivity due to BD**

Hypothesis: a single t-PBM session on the R-dlPFC will significantly increase BOLD-signal at the R-dlPFC, relative to sham.

2. **To test the effect of repeated t-PBM sessions on CBF, after irradiating R-dlPFC, in subjects with impulsivity due to BD**

Hypothesis: repeated t-PBM sessions on the R-dlPFC will significantly increase BOLD-signal at the R-dlPFC at day 5 relative to baseline.

3. **To test the effect of repeated t-PBM sessions on impaired decision making, in subjects with impulsivity due to BD**

Hypothesis: repeated t-PBM sessions on the R-dlPFC will significantly improve decision making − increase in net gain at the Iowa gambling task, decrease in Barratt Impulsiveness Scale (BIS) score at day 5 and follow-up visit relative to baseline, decrease in BRIEF-A score at day 5 and follow-up visit relative to baseline, and a decrease in I-7 Impulsiveness and Venturesomeness Questionnaire score at day 5 and follow-up visit relative to baseline.

4. **To test the effect of repeated t-PBM sessions on manic symptoms (MOODS-SR) in subjects with BD**

Hypothesis: repeated t-PBM sessions on the R-dlPFC will significantly decrease the total Mood Spectrum-Self Report (MOODS-SR) score at day 5 and follow-up visit relative to baseline. Dimensional improvements will be analyzed as a secondary step.

3. General Description of Study Design

This is a single-blind study to test the neuropsychological and clinical effects of t-PBM with NIR in BD. For our primary aim of examining the effect of tPBM on CBF, the study is additionally sham-controlled. Twenty patients with a diagnosis of bipolar disorder, not currently in a depressive, manic, or mixed state episode, will undergo one sham and one NIR- t-PBM session on day 1 (within MRI scanner), and one daily NIR- t-PBM session from day 2 to 5. On day 5, the NIR t-PBM session will also occur in the MRI scanner. The fMRI scan will measure BOLD changes during sham t-PBM (day 1) and during NIR t-PBM (day 1 & 5), on R-dlPFC. Impulsivity will be assessed by the BIS at pre-screen (for inclusion criteria), baseline, treatment day 5, and the follow-up visit; and by the gambling tasks at baseline, after the first NIR t-PBM (day 1), after the fifth NIR t-PBM (day 5), and at the follow-up visit. Other aspects of impulsivity and executive functioning will be assessed by the I-7 and BRIEF-A at baseline, day 5, and the follow-up visit. The MOODS-SR-Last Week will be administered at baseline, day 5, and the follow-up visit to assess change in mood, particularly hypomanic symptoms. At screening, subjects will complete the MOODS-SR Lifetime.

4. Subject Selection

We intend on enrolling 30 subjects diagnosed with bipolar disorder, with the goal of randomizing 20 subjects.

Inclusion criteria for this study include: 1) adults between the ages of 18 and 65, 2) diagnosis of bipolar disorder assessed with M.I.N.I. diagnostic interview, 3) currently experiencing symptoms of impulsivity as per BIS total cut-off score equal or greater than 70, 4) if of child-bearing potential must agree to use adequate contraception (e.g. oral contraceptives, intrauterine device, double barrier methods, or total abstinence from intercourse), and 5) vision corrected to normal with contacts/vision does not require glasses or other visual aids.

Exclusion criteria for this study include: 1) currently in depressive, manic, or mixed episode; 2) currently psychotic; 3) judged to be at serious and imminent suicidal risk (C-SSRS≥4); 4) currently in alcohol or substance use disorder (meeting criteria in the past 3 months as assessed with M.I.N.I. diagnostic interview); 5) unstable medical conditions; 6) inability to consent or to complete study procedures; 7) failure to meet standard MRI safety requirements (e.g. claustrophobia, non-removable piercings, implanted medical devices, other non-removable metals) as determined by the MRI Safety Checklist; 8) changes in medications or use of augmentative devices and other interventions in the 2 weeks prior to the study; 9) participation in other clinical research trials that may influence primary outcomes or adherence to the proposed study, as assessed by the PI and the Co-Is; and 10) current pregnancy.

Source of subjects will include outpatient clinics at MGH and McLean, the Translational and Clinical Research Center, and Registries/Patient Databases such as the RPDR and Patient Gateway Announcements and or Invitations. We will recruit primarily through referrals from physicians, flyers, online advertisements, and platforms such as Partners Rally and ResearchMatch. We will respond to all individuals who express interest in the study, whether it is from an online recruitment source or through a referral from outpatient clinics at MGH. Clinical research coordinators will primarily handle recruitment and outreach, though some tasks may fall to other members of study staff, like interns. Physicians may send referrals directly to Dr. Cassano, who will forward the information to a CRC to make contact.

We will not discriminate against any group of persons. Based upon the composition of the patient population at MGH and Boston, we anticipate that at least 50% of the participants will be women. The percentage of minority participants is expected to be at least 20%, consistent with previous studies in our lab and at MGH. We expect a roughly equal distribution across sex and ethnicity, as has been previously demonstrated with BD, with the potential for slightly more diagnoses of BD type-I among men and BD type-II among women. Fetuses, children, prisoners, and institutionalized individuals will not be recruited, because they are beyond the scope of the objectives. We will review recruitment regularly at team meetings to track progress and adjust recruitment strategies as needed.

We are only enrolling English-speaking participants in this study since the measures used are developed and validated in the English language and because non-English speaking subjects may not be able to understand study procedures, which could undermine the validity of the results.

5. Subject Enrollment

Individuals interested in participating in the study will contact study staff through online recruitment platforms, such as Partners Rally and ResearchMatch. Additionally, patients may be referred to the study from outpatient clinics at MGH. All interested individuals will undergo a screening by trained study staff to ensure eligibility and, importantly, their capacity for voluntary, informed consent. Study staff will describe the study and go through informed consent procedures. Subjects will read the consent form without any time constraints and will be provided the opportunity to ask any questions related to study procedures. Individuals will be officially enrolled upon signing the consent form. This study will not change the clinical care that subjects receive, meaning that all subjects participating in the study will receive the same clinical care as those who are not.

Individuals interested in participating will first be phone-screened for eligibility prior to signing the consent form. The PI and licensed physician co-Investigators with detailed knowledge about the study aims, logistics, procedures, risks, benefits, and alternatives will obtain written informed consent from subjects who meet criteria for this study. Individuals will be given the opportunity to take time to consider participation prior to signing the consent form. Since Dr. Ellard's patients might be offered the participation in this study, the PI, Dr. Cassano, or other licensed co-Is will review the consent and co-sign the consent for any study subjects referred to the study by Dr. Ellard. This measure will be implemented to prevent any type of coercion.

All subjects participating in the study will receive the same standard of care as those who are not. There are additional study procedures that subjects will undergo, though this should have little to no impact on clinical care. Further, study participation will not impact access to standard of care, meaning that participating in the study will not prohibit subjects from receiving standard treatments for bipolar disorder.

t-PBM is not considered standard of care and is therefore an alternative treatment for bipolar disorder. Standard of care for bipolar disorder includes, but is not limited to, psychotherapy, medications (such as mood stabilizers, anti-depressants, or anti-psychotics), or device-based treatments (such as ECT). Information on standard of care for bipolar disorder will be provided to all subjects. Subjects may continue with their current treatment regimen throughout the study.

The MGH Brain Photobiomodulation Clinic (Director: Paolo Cassano, MD PhD) has historically served as a resource for subjects enrolled in t-PBM clinical trials who then wish to continue with specialized supervision. Study staff will offer access to the clinic to all subjects upon study completion.

Participants will be compensated $125 for each of the following visits: Baseline, Treatment 1, Treatment 5, and Follow Up. For each of these visits, the participant receives $25 for attending the appointment, $50 for completion of the first gambling task, and $50 for the completion of the second gambling task. Participants who complete all portions of the study will receive a total of $500. Subjects who end study procedures prematurely will be compensated for all completed study procedures. Subjects will be mailed a check at the conclusion of their study participation.

While participants will always receive the full $50 for completing each gambling task, they will be told that their real-world earnings are based on their performance on the gambling task. They will be told that the maximum amount of real-world money that they can earn in each task is $50. Participants will be told that the better they do on the task, the closer they will get to earning the full $50, and that their total earnings will be revealed at the final study visit. The purpose of these gambling tasks is to investigate various aspects of behavior, such as impulsivity and decision-making. In order for these tasks to effectively gather accurate data on these behaviors, it is crucial that the participants believe that the amount of money they earn is based on their decisions within the task. Upon completion of all study procedures, participants will be informed that they will receive the full $50 for each of the eight gambling tasks that they completed.

This deception may result in increased frustration related to performance on the gambling tasks. This deception involves no more than minimal risk to the participants.

If participants do not believe that their compensation is affected by their performance on the gambling tasks, they will not be sufficiently motivated to perform to the best of their ability. The promise of a monetary reward will create a more realistic model of real-world decision making and impulsivity, which are the behaviors that these tasks are designed to measure. This deception is therefore necessary in order to obtain worthwhile data.

This deception will be disclosed by study staff at the end of the follow up visit. Participants will receive a debriefing form explaining the reasoning for a nature of the deception.

6. STUDY PROCEDURES

Study Visits

Contact with potential participants

Initial contact made with potential research subjects will include only the minimum PHI (name and email). Study staff will obtain written or verbal consent to continue correspondence through unencrypted emails or will send detailed study and PHI information using the "Send Secure" function. Emails not sent using "Send Secure" to participants will contain and automatic email signature alerting them that the email is not encrypted. If participants are uncomfortable receiving information unencrypted, they should alert study staff who will then proceed to communicate securely with the participant. If an individual contacts the study staff by email first, it is implied that email communications are acceptable. Study staff will verify that individuals are comfortable with unencrypted emails and obtain written or verbal consent to proceed with unencrypted email communication.

Pre-Screen

Prior to enrolling in the study, interested individuals will be contacted by trained study staff for a pre-screening, which can be completed over the phone or via a REDCap link. The trained study staff will review study details and procedures and will ask a series of questions and administer

two questionnaires (the ASRM and the PHQ-9) to assess eligibility for the study. Additionally, study staff will either administer the Barratt Impulsiveness Scale (BIS) over the phone or send interested individuals the REDCap survey link to assess if their impulsivity levels meet our inclusion criteria. Prior to collecting any information, individuals will be asked to provide verbal authorization to write down their responses and will be given the option to not answer questions if they do not wish to do so. Individuals will also be given the opportunity to provide verbal consent regarding unencrypted emails. If the individual is eligible for the study, they will be invited to a screening visit. If the individual is not eligible or decides not to enroll, any information collected during the phone call will be destroyed to protect privacy. If an individual is eligible for the study and enrolls, the information collected during the pre-screening phase will be added to their research file. Individuals will be sent a copy of the consent form for their review via email and the screening visit will be scheduled. Individuals will be reminded not to discuss medical information through unencrypted emails. Individuals will be instructed not to sign the consent form until after they've discussed it with the clinician during the screening visit.

Screening

Subjects will review the consent form with the study clinician (PI or Co-I; MDs) and be given the opportunity to ask questions. Consent will be obtained by a licensed physician investigator. If the screening visit is conducted remotely using Zoom, the consent form will be collected electronically using REDCap following the MGH eConsent Template. Subjects will then receive an electronic copy of the consent form through their provided email which they can download and keep for their records. This is an automatic function of REDCap. If the screening visit is conducted in-person, the consent form may be collected on REDCap or on paper. If the consent form is signed on paper, subjects will receive a paper copy of the consent. Subjects will be considered enrolled in the study once they sign the consent form.

Subjects will be asked a series of questionnaires to assess eligibility for the study, including the Mini International Neuropsychiatric Interview (MINI), and the Columbia Suicide Severity Rating Scale (C-SSRS). Demographic information, concomitant medications and therapies, prior treatment history, and medical history will be collected. Subjects will complete an MRI Screening Form and the MOODS-SR Lifetime. Screening will also include a dipstick toxicology urinalysis and, if applicable, a dipstick pregnancy test. If the subject is eligible, they will be invited to continue to the baseline visit. If not eligible, the subject will not be invited to continue with the study.

Baseline Visit

Adverse events, as well as concomitant medications and therapies, will be collected. Participants will complete the Young Mania Rating Scale (YMRS), the BIS, the BRIEF-A, the I-7, the CAST-IRR, and the SAFTEE. A licensed clinician will administer the C-SSRS and the CGI-S. Skin color will be recorded using the NIS-SCS. Participants will complete two computerized gambling tasks: The Iowa gambling task and the Delgado gambling task. The order of administration of the gambling tasks will be randomized. This appointment will last approximately 90 minutes.

Treatment 1

Vitals will be assessed and recorded. The MRI Safety Checklist will be completed and signed before the MRI. Participants will undergo an MRI Scan. While in the scanner, participants will first undergo a structural scan and resting state scan, followed by a functional scan during which the participants will receive a sham t-PBM treatment. This scan will be followed by a pre-stimulation resting-state functional acquisition. At this time, active t-PBM will be administered, immediately followed by a post-stimulation resting state scan. Participants will then complete the Delgado gambling task. A functional sequence will be collected during the administration of the gambling task. Finally, participants will undergo a post-stimulation resting state functional scan. The MRI will last approximately 75 minutes in total.

Participants will know that they are receiving both active and sham treatment, but they will not be told in which order the treatments will be delivered. Participants will complete the PBQ, CAST-IRR, TSRQ, and the Iowa Gambling Task at the conclusion of the visit. Study staff will complete an intervention tracking form.

Treatments 2-4

Treatments 2, 3, and 4 should ideally occur once daily during the three days following the first treatment administration. If necessary, this window can be extended so that these three treatment visits occur within ten days of the Baseline/Treatment 1 visit (in this case, the timing of follow up visits will be adjusted accordingly). Adverse events and concomitant medications and therapies will be assessed and recorded at each visit. Participants will complete the TSRQ and CAST-IRR after treatment administration. Study staff will complete an intervention tracking form for each study visit.

Treatment 5

Treatment 5 should ideally occur the day after Treatment 4. If necessary, this window can be extended so that this visit occurs within ten days of the Treatment 1 visit (in this case, the timing of follow up visits will be adjusted accordingly). Adverse events, concomitant medications and therapies, and vitals will be assessed and recorded. The MRI Safety Checklist will be completed and signed before the MRI. Participants will complete the MOODS-SR, the BIS, the BRIEF-A, and the I-7.

Participants will undergo an MRI Scan. A structural scan and a pre-stimulation resting state functional scan will be collected first. Active t-PBM will be administered immediately after the resting-state scan, followed by a post-stimulation resting state functional scan. Participants will then complete the Delgado gambling task. A functional sequence will be collected during the gambling task administration. The MRI will last approximately 45 minutes in total.

Participants will complete the SAFTEE, the CAST-IRR, the TSRQ, and the Iowa gambling task after the MRI/t-PBM session. Study staff will complete an intervention tracking form.

Clinical Check-in Call

A licensed study clinician will call the participant (phone or video call) approximately 2-3 days after the final treatment session. Adverse events and concomitant medications and therapies will be assessed and recorded. The clinician will administer the C-SSRS and the CGI-S/I. The clinician may use the PHQ-9 and/or ASRM to guide their call with the study participant, though these scales do not need to be completed in full. The purpose of this call is to check in on the general safety and well-being of the participant.

Follow Up Visit

The follow up visit takes place approximately one week after the final treatment session. This visit will be completed in person. Adverse events and concomitant medications and therapies will be assessed and recorded. Participants will complete the MOODS-SR, the BIS, the BRIEF-A, the I-7, the SAFTEE, the Delgado gambling task, and Iowa gambling task. The order of administration of the gambling tasks will be randomized. A licensed clinician will administer the C-SSRS and the CGI-S/I.

Communication with participants throughout the study:
Participants who consent to text messaging, in addition to standard email and phone communication, will receive a text message reminder before every scheduled visit. Text messages will be sent via Updox Secure Text Messaging and SMS. Updox is an online messaging service that specializes in secure healthcare communication.

Participants who consent to text messaging will receive a text message the day before each scheduled study visit. This message will be sent as a SMS text message letting the participant know they have received a secure message from the MGH Photobiomodulation Lab with a link to access the message. The first message received will instruct them to enter in their full name and create a PIN to access the message. Each time a message is received they must enter their unique PIN number to access the message. Study staff do not have access to anyone's personal PIN numbers. Individuals are able to respond back to the message they receive with questions or for more information if necessary.

tPBM Administration

The t-PBM-NIR device used in the study is the Litecure's LightForce® EXPi Deep Tissue Laser Therapy ™ System, Transcranial PhotoBioModulation-1000 (tPBM-2.0). The tPBM-2.0 is an investigational device based on LiteCure's LightForce® EXPi Deep Tissue Laser Therapy ™ System. For the investigational study, the EXPi System's beam delivery - Empower ™, is modified to non-invasively deliver Near-Infrared Radiation (NIR) to subjects diagnosed with Bipolar Disorder. The modified system is also configured to provide sham (placebo) treatment. The device is manufactured and supplied by LiteCure LLC, 101 Lukens Dr, Suite A, New Castle, DE 18720.

The treatment program (using the parameters outlined below) will be programmed into the device. The console displays the time and energy delivered and automatically turns itself off once the treatment is completed.

Table 1. tPBM Parameters

Measure (unit)	**Value**
Wavelength (nm)	808nm
Exposure time (s)	333
Area of exposure (cm^2)	24
Irradiance, Power Density (mW/cm^2)	300
Fluence (J/cm^2)	100
Total Energy (kJ)	2.4
NIR Source	Laser
Laser Output (W)	3.5 per fiber (7 total)
Wave Mode	Continuous
Anatomical Targets	F4 & F8 (proximity)
Device	Litecure's LightForce® EXPi Deep Tissue Laser Therapy ™ System, Transcranial PhotoBioModulation-1000 (tPBM-2.0)

The tPBM-2.0 is considered a Class II medical device per 21 CFR 890.5500 and 878.4810 and is manufactured per 21 CFR 820. It utilizes a laser diode source with a maximum continuous (CW) output of ≤30 Watts at a wavelength of 808 nanometers (nm) and nominal beam diameter of 40mm at the outside aperture.

The tPBM-2.0 consists of a therapeutic laser console (that produces laser energy as NIR), and an optical delivery system consisting of a flexible, double-sheathed optical fiber connected to a custom helmet (cap). The cap is configured to deliver NIR light to EEG site F4 (or in close proximity if covered by hair), covering a total surface treatment area of approximately 24 cm^2 [12 cm2 x 2]. It also includes laser safety eye ware with an optical density rating >5.0 at 808 nm.

The therapeutic laser console is the only component of the device that is not MRI compatible. It will be stored in an equipment room located in Zone 2 (area with no detectable magnetic field but to which access is restricted due to scanner proximity). An MRI-compatible optical fiber will connect the laser console to the MRI-compatible cap. The safety eye wear is also MRI compatible.

Aside from the cap, the tPBM-2.0 is the same device as LiteCure's EXPi System – Model LTS-2500, which is marketed under FDA's 510(K) # K107637.

The cap is a custom 3D-printed headgear made of plastic and serves to hold the laser probe in place, between the MRI coil and the subject's head. The cap is provided by the device manufacturer (LiteCure) and is very similar to those used in our previous t-PBM studies. The laser probe (attached to the cap) will be connected to the laser console with a multimode MR-compatible optical fiber. The distal end of the optical fiber is fitted with ceramic ferrules, which will be affixed to the cap. The cap (headgear) contains clamps which secure the ferrules. The cap will be used in place of the wand. The cap is the only modification of the device delivery system, and it was required in order to do the t-PBM inside the MRI scanner. The cap is a component of the tPBM-2.0 device; it is not a separate device. The cap is used to apply NIR to EEG site F4.

The t-PBM-2.0 is a nonsignificant risk device because it:

1. Is NOT intended as an implant and DOES NOT present a potential for serious risk to the health, safety, or welfare of a subject;
2. Is NOT purported or represented to be for a use in supporting or sustaining human life and DOES NOT present a potential for serious risk to the health, safety, or welfare of a subject;
3. Is NOT for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and DOES NOT present a potential for serious risk to the health, safety, or welfare of a subject; or
4. DOES NOT otherwise present a potential for serious risk to the health, safety, or welfare of a subject.

Further,

- The t-PBM-2.0 maximum dose administered in this study does not exceed the Maximum Permissible Exposure (MPE) for skin – Center for Devices and Radiological Health (CDRH), 21CFR1040.10 and 21CFR1040.11;
- The t-PBM-2.0 is substantially equivalent to the OmniLux New U which the FDA has already categorized as a non-significant risk device;
- Currently FDA-cleared lasers are typically available over-the-counter and are considered safe to use without professional supervision.
- The MGB IRB determined a similar PBM device as NSR for the ELATED-3 study (IRB Protocol Number 2016P001490). The ELATED-3 device operated at significantly higher irradiances than the current PBM device. The FDA determined that an IDE was not required for the ELATED-3 device.
- The current PBM device was deemed to be NSR by the NYU Langone Health IRB in previous studies.

The tPBM-2.0 device is currently being used in two other approved studies at MGH: Transcranial Photobiomodulation for Alzheimer’s Disease (Protocol #2020p003051) and Transcranial Near Infrared Radiation and Cerebral Blood Flow in Depression (Protocol #2020p000845).

Safety data from the use of the t-PBM 2.0 device in currently active studies at the time of initial review

TRIADE (Protocol #2020p000845) – Adverse Events: As of May 4th, 2022, Cumulative data from all three study sites

Adverse Event	Number Participants	Number Incidences	Severity	Study Intervention Relationship	Resolved	Expected
			Mild= 1 Moderate= 2 Severe= 3	1= Not related 2 = Unlikely 3 = Possibly 4 = Probably 5 = Definitely	1= yes 0= No	1= yes 0= no
SKIN WARMING	9	12	1,1,1,1,1, 1,1,1,1,2, 1,1	5,5,3,4,4, 4,4,5,3,5 5,4	1,1,1,1,1, 1,1,1,1,1 1,1	1
INSOMNIA	3	4	2,1,2,2	3,4,3,4	1,1,1,0	1
EARLY MORNING AWAKENING	1	1	3	4	1	1
DISCOMFORT DURING MRI	2	2	1,2	5,3	1,1	1
PANIC ATTACK DURING MRI	1	1	2	4	1	1
ANXIETY DURING MRI	1	1	1	1	1	1
HEADACHE	8	8	1,2,1,2, 2,1,2,1	1,3,3,3, 1,1,4,4	1,1,1,1, 1,1,1,1	1
CLAUSTROPHOBIA	1	1	1	4	1	1
BLURRY VISION	1	1	1	2	1	0
SEIZURE	1	1	2	2	1	0
PANIC ANXIETY	3	3	1,1,2	4,1,1	1,1,1	1,0,1
PAIN ON FOREHEAD	1	1	1	4	1	1
BURNING SENSATION ON SKIN	1	1	2	5	1	1
PANIC ATTACK WITH DISSOCIATION	1	1	1	0	1	0
RENAL INFECTION	1	2	3,3	1,1	1,1	0,0
MOTOR VEHICLE ACCIDENT (NO PHYSICAL INJURY)	1	1	1	1	1	0
NIGHTMARES	1	1	1	4	1	1
STYE	1	1	1	3	1	0

WORSENING ANXIETY	1	1	2	2	0	1
"MIND FOG" AFTER MRI	1	1	1	4	1	1

TRAP-AD (Protocol #2020p003051) – Adverse Events: As of May 4th, 2022, Cumulative data from all three study sites

ADVERSE EVENT	NUMBER PARTICIPANTS	NUMBER INCIDENCES	SEVERITY	STUDY INTERVENTION RELATIONSHIP	RESOLVED	EXPECTED
			Mild= 1 Moderate= 2 Severe= 3	0= Not related 1 = Unlikely 2 = Possibly 3 = Probably 4 = Definitely	1= yes 0= No	1= yes 0= no
ANKLE EDEMA	1	1	3	0	1	0
CHEST TIGHTNESS	1	1	3	0	1	0
DIARRHEA	2	2	1,1	0,0	1,1	0,0
DIZZINESS	3	4	1,1,1,1	1,0,2,2	1,1,0,1	0,0,1,1
FATIGUE	2	2	1,1	1,2	0,0	0,1
FEELINGS OF UNEASINESS	1	1	1	2	1	0
HEAD WARMING	3	13	1,1,1,1,1, 1,1,1,1,1, 1,1,1	4,4,4,4,4, 4,4,4,4,4, 4,4,4	1,1,1,1,1, 1,1,1,1,1, 1,1,1	1,1,1,1,1, 1,1,1,1,1, 1,1,1
HEADACHE	2	2	1,1	2,3	0,1	1,1
INSOMNIA	1	2	1,1	2,0	1,0	1,1
ITCHINESS ON UPPER BACK	1	1	1	0	0	0
JAW PAIN/TEETH CLENCHING DURING SLEEP	1	1	1	1	0	0
LIGHTHEADEDNESS	1	1	1	0	1	0
POSITIONAL VERTIGO IN MRI	1	1	1	0	1	1

RASH (UPPER BACK)	1	1	1	1	1	1
SEEING LIGHT DURING TREATMENT	1	1	1	4	1	1
SKIN REDDENING	3	27	1,1,1,1,1, 1,1,1,1,1, 1,1,1,1,1, 1,1,1,1,1, 1,1,1,1,1 1,1	4,4,4,4,4, 4,4,4,4,4, 4,4,4,4,4, 4,4,4,4,4, 4,4,4,4,4, 4,4	1,1,1,1,1, 1,1,1,1,1, 1,1,1,1,1, 1,1,1,1,1, 1,1,1,1,1, 1,1	1,1,1,1,1, 1,1,1,1,1, 1,1,1,1,1, 1,1,1,1,1, 1,1,1,1,1, 1,1
Skin warming (forehead)	6	22	1,1,1,1,1 11,1,1,1, 1,1,1,1,1, 2,1,1,1,1, 1,1	4,4,4,4,4, 4,4,4,4,4, 4,4,4,4,4, 4,4,4,4,3, 4,4	1,1,1,1,1, 1,1,1,1,1, 1,1,1,1,1, 1,1,1,1,1, 1,1	1,1,1,1,1, 1,1,1,1,1, 1,1,1,1,1, 1,1,1,1,1, 1,1
Stomach Discomfort	1	1	1	1	1	0
Vivid Dreams	2	2	1,1	2,2	1,1	1,1
Vomiting	1	1	1	0	1	0

Assessments

Adverse Events Form

The Adverse Events Form captures any adverse event (serious or otherwise) that the subject experiences while participating in the study. Events may occur during or outside of study procedures.

Altman Self-Rating Mania Scale (ASRM)

The ASRM is a 5-item self-rated mania scale designed to assess the presence and/or severity of manic symptoms over the past 7 days. This scale will be administered as part of the pre-screening phase.

Barratt Impulsiveness Scale (BIS)[39]

The BIS is a 30-item measure of cognitive and motor impulsivity rated on a 4-point Likert scale (1 = rarely/never to 4 = almost always/always). It captures three factors: Motor Impulsiveness, Non-Planning Impulsiveness, and Attentional Impulsiveness. The BIS has demonstrated high internal consistency and validity across populations.

Behavior Rating Inventory of Executive Function – Adult Version (BRIEF-A)[40]

The BRIEF-A is a 75-item self-report scale to assess executive function. It consists of two indices: The Behavioral Regulation Index and the Metacognitive Index. The Behavioral Regulation Index measures inhibition, set shifting, control, and attention monitoring. The Metacognitive Index measures ability to initiate tasks, working memory, planning/organization ability, task monitoring, and organization. The BRIEF-A has demonstrated good internal consistency and validity across several clinical populations and non-clinical controls.

Concise Associated Symptom Tracking Irritability Scale (CAST-IRR)

This instrument is a five item self-report that assesses irritability over the last 24 hours.

Clinical Global Impressions – Severity and Improvement (CGI-S, CGI-I)

These two instruments are scored 1-7 by the clinician based on assessment of the subject's overall clinical status. They measure, based on history and scores on other instruments:
(a) severity of impairment (CGI-S) and (b) clinical improvement (CGI-I).

Columbia Suicide Severity Rating Scale (C-SSRS) [41]

An instrument endorsed by the FDA for clinical trials. This instrument systematically tracks suicidal ideation and behavior (e.g., suicide attempts, wish to die, thoughts of suicide, plan, and intent).

Concomitant Medications and Therapies Form

This form records all ongoing medications, as well as other therapies, and will be completed at every study visit, including the screening visit, as a safety-monitoring tool.

Iowa Gambling Task

In this computerized task, participants play a game of chance in which they can win or lose fake money. Participants are presented with four cards and are asked to choose one. Their choice results in a gain or loss. Participants are given feedback on each choice. This task is designed to measure impulsivity.

Delgado Gambling Task (IGT)

In this computerized task, participants play a game of chance in which they can win or lose fake money. Participants are given a target number. They are then presented with a sequence of cards. Before each card is presented, participants are asked to guess whether the number on the next card will be higher or lower than the target number. They are then given feedback on their choice. This task is designed to measure reward-processing.

I-7: Impulsiveness and Venturesomeness Questionnaire

The I-7 is a self-report scale of 54 items and three subscales. Of the 54 items, 19 measure Impulsiveness, 16 measure Venturesomeness, and 19 measure Empathy. Answers are marked as "Yes" or "No."

Mini International Neuropsychiatric Interview (M.I.N.I)[42]

The M.I.N.I. is a short structured diagnostic interview, developed jointly by psychiatrists and clinicians in the United States and Europe, for DSM and ICD psychiatric disorders. With an administration time of approximately 15 minutes, it is designed to meet the need for a short but accurate structured psychiatric interview for clinical trials. According to researchers at the National Institute of Mental Health's (NIMH) Division of Clinical and Treatment Research, the M.I.N.I. is a fully validated and more time-efficient alternative to the Structured Clinical Interview for DSM Disorders (SCID). For the purposes of this study, we will only use modules related to mood, psychosis, and substance abuse.

MOODS-SR – Last Week & Lifetime

This 161-item self-report scale assesses manic-depressive symptoms. Participants are asked to answer "Yes" or "No" to each question. Subdomains measure Moods, Energy, Cognition, and Rhythmicity. Time frame is either lifetime or the last week, depending on scale used.

MRI Safety Checklist

This form identifies risk factors that may make MRI participation unsafe.

New Immigrant Survey-Skin Color Scale (NIS-SCS)[43]

The NIS-SCS is an 11-point scale, ranging from zero to 10, with zero representing albinism, or the total absence of color, and 10 representing the darkest possible skin. The ten shades of skin color corresponding to the points 1 to 10 on the Massey and Martin Skin Color Scale are depicted in a chart, with each point represented by a hand, of identical form, but differing in color. The respondent never sees the chart. We gather this data for use as a potential covariate in analyses as skin color can affect absorption of NIR.

Patient Health Questionnaire (PHQ-9)

This nine-item self-report measure assesses the presence and severity of depressive symptoms over the past 14 days. This scale will be administered as part of the pre-screening phase.

Perceived Blinding Questionnaire (PBQ)

The PBQ is a self-report questionnaire to determine the degree to which the participant believes they are receiving active treatment or sham.

Prior Treatment Log

This form captures information regarding prior treatments for bipolar disorder or other mental health concerns.

Systematic Assessment for Treatment Emergent Events (SAFTEE)[44]

The SAFTEE is a commonly used instrument originally developed by NIMH and adapted into a self-report instrument. The version of the scale that we plan to use is the same used by the multi-center, NIMH-sponsored CO-MED trial, and it examines in a systematic fashion all possible treatment-emergent side effects and probes specific adverse symptoms, including suicidal thoughts and behaviors, and self-injurious behavior.

t-PBM Self-Report Questionnaire (TSRQ)

An open-ended questionnaire focusing on potential inconveniences and discomforts from the t-PBM treatment.

Young Mania Rating Scale (YMRS)

This 11-item clinician-rated scale is used to assess the presence and severity of manic symptoms.

MRI Scanning

The collection of MRI images will take place in a 3T magnet scanner with multi-channel receivers. All protocols have been developed and validated at the Martinos Center for biomedical imaging.

Participants will undergo conventional high-resolution 3D T1-weighted MPRAGE scans, resting state functional connectivity MRI sequences, and task-based functional connectivity MRI sequences.

We will examine areas pertaining to impulsivity, mood, and executive function, including but not limited to the Salience Network, Central Executive Network, Limbic Areas, Default Mode Network, and the dlPFC.

This data will be used to test the effect of a single t-PBM session on cerebral blood flow (CBF), while irradiating R-dlPFC (SA1), in subjects with impulsivity due to BD and to test the effect of repeated t-PBM sessions on CBF (SA2).

7. Risks and Discomforts

Screening and Evaluation: The risks and discomforts of the screening evaluations include discomfort or distress responding to potentially sensitive questions regarding mental illness and drug use. Research interviews are interrupted if individuals become distressed or object to answering questions.

Delay in Initiation of New, or Changes in Ongoing, Bipolar Treatment: While this study is not testing t-PBM as a treatment for bipolar disorder, it is possible that participants will experience improvements to their symptoms while undergoing t-PBM. Any delay in receiving t-PBM (while screening procedures are completed) might be considered as a delay in treatment from a patient perspective. We will emphasize that the study is not geared to test a treatment but instead the impact of t-PBM on cerebral blood flow.

Further, study participation requires stable BD treatment during and two-weeks prior to enrollment. Subjects should not change medications, treatments, or therapeutic interventions two weeks prior to study enrollment or during study participation as to avoid interference with t-PBM treatment. However, without adjustment of medication it is possible that participants' symptoms may worsen while participating in the study. This may include increased disturbances in mood, anxiety, sleep, appetite, energy, or cognition. This could result in work loss, loss of social function, and possibly increased risk of suicide. Therefore, there is some risk to halting medication changes while in the study. However, the risk will be minimized as there are several safety precautions in place and participants will have frequent contact with study clinicians. The clinical monitoring in this study exceeds that of standard care for BD. The potential benefits of improving impulsivity and cognition offset the risk of worsening BD symptoms.

Risks of Clinical Decompensation: If a patient has worsened to such a degree that further participation would put them at risk, then they will be discontinued from the study. In such cases, the patient is immediately transferred to standard clinical treatment and exited from the research.

At any point during the study, patients are told to immediately inform their study psychiatrist if they develop worsening of depression or anxiety, symptoms of mania or psychosis, or active suicidal plans.

Suicidality Standard Operating Plan (SOP): If a subject spontaneously expresses suicidal ideation and the thoughts are passive, vague, or infrequent, the study team will respond with close monitoring of the subject. This may include phone calls, video calls, or in-person check-ins between the study clinician and the subject. If the suicidal ideation includes more specific thoughts, intent, and/or plans, if the subject responds "Yes" to questions 4 or 5 of the C-SSRS, or if the subject answers 1, 2, or 3 to Question 9 of the PHQ-9, then they will be proactively discontinued from the study and referred to adequate care.

Risks associated with study tasks: Performing tasks can result in frustration related to difficulty with performance, or boredom during longer sittings. Participants may refuse to answer questions that make them uncomfortable.

Risks of Magnetic Resonance Imaging: MRIs use powerful magnets to make images. There are no known radiation risks associated with MRI. However, individuals with metal implants, such as surgical clips or pacemakers, should not have an MRI. All credit cards and other items with magnetic strips should also be kept out of the MRI room. People who feel uncomfortable in confined spaces (claustrophobia) may feel uncomfortable in the narrow tube. The MRI makes loud banging noises as it takes images. Earplugs can be used to reduce the noises. The MRI can be stopped at any time at subject's request. If the study subject is or suspects they are pregnant, they should not participate in this study. Study staff will assess chance of pregnancy. If there is any uncertainty, a study physician can recommend a pregnancy test. The MRI has the potential, during normal routine use, to cause localized warming of participant's skin and of the underlying tissues. The participant will be instructed to immediately inform study staff if they experience discomfort due to warming and the procedure will be stopped.

Some people experience dizziness or rarely nausea when going into an MRI scanner and these sensations may be more common in scans with higher magnetic fields. In most cases, these symptoms only last a short time. However, some people may experience them throughout the scan and/or continue to experience them for a short period of time after (generally, less than half an hour). No case of permanent problems is known.

Risks of tPBM: The study laser device emits light with a longer wavelength than the human eye can see. The staff will be provided training on basic safety procedures relative to the use of the device. The staff administering the t-PBM will be careful not to operate the laser unless it is in direct contact with the subject's skin. Protective eyewear is required since the device is a laser. Failure of laser device, resulting in the cessation of investigative therapy can cause no adverse event to our knowledge. Delivery of the infrared laser energy to an inappropriate site, such as directly over the open eye, would pose risk to the subject, such as blindness. Based on previous observations with similar laser devices, application of the laser may result in mild thermal sensation of warmth during use. The temperature of the skin is however kept well below the level for thermal damage. Based on human clinical trial experience to date and on sale of t-PBM devices for their intended use (e.g. Omnilux New-U), each adverse event listed below has been

reported by less than 0.1% of all subjects and users: erythema, pain, discomfort, warmth, headache, or other reactions at the application site. In our research experience, t-PBM devices could produce insomnia, irritability, and fleeting illusions. The modality of administration for t-PBM with the study laser device is analogous to the protocols used in our feasibility studies. The dose of light delivered by the study device is analogous to our feasibility studies and to published studies on t-PBM. No serious adverse events occurred during our feasibility trials.

8. Benefits

The effects of the current proposal on impulsivity in individuals with bipolar disorder are yet unknown. It is possible that subjects may experience improvements in impulsivity, cognition, or other symptoms of bipolar disorder. Participants in this study will improve our understanding of the pathology underlying bipolar disorder and their participation may lead to the development of novel therapeutics.

9. Statistical Analysis

Preprocessing of MRI and fMRI data will be performed with the FreeSurfer software package, scripted in Bash. Slice-time correction, motion-correction, and co-registration of functional BOLD scans, Time of Repetition (TR), and participant will then be performed. BOLD signals will then be smoothed to a full-width half maximum (FWHM) of 3mm and z-scored at every voxel.

t-PBM related increase of BOLD percent signal change (PSC) averaged across all ROI voxels will be assessed during the first scanning session where the participant receives both sham and NIR over the R-dlPFC. PSC of t-PBM related increase in BOLD both during and after stimulation will be the dependent variable with the independent variable being the condition of t-PBM during the first session (sham vs. NIR).

BOLD signal will again be assessed during the 5^{th} NIR session as a PSC across all ROI voxels in comparison with the BOLD PSC from the first NIR session to observe any BOLD changes after 5 NIR treatment sessions. The dependent variable will the BOLD signal and the independent variable will be the timepoint: day 1 vs. after 5 sessions (day 5).

For both gambling tasks, the gambling task net gain score will be analyzed for changes from baseline to after treatment on day 1, baseline vs day 5, and baseline vs follow up. The BIS, BRIEF-A, and I-7 will be analyzed for changes from baseline to day 5 and follow up. Here, the dependent variable will be the gambling tasks' net gain scores, BIS, BRIEF-A, and I-7 total score. The independent variable is the timepoint baseline vs. day 5 (for the gambling tasks) and follow up.The MOOD-SR will also be analyzed for a decrease in impulsivity at each timepoint of baseline vs. day 5 and follow up. A General Mixed Models Regression will be used with time as a fixed effect and subject as a random effect.

Secondary analyses will also be performed for the BIS, BRIEF-A, I-7, MOOD-SR, SAFTEE, and TSRQ. Each scale and their respective subscales will be analyzed for specific changes at

each timepoint to better understand the effect t-PBM NIR has on the symptoms and presentation of BD. These additional analyses will also be helpful in assessing the initial safety profile of t-PBM in this psychiatric population.

Power and Detectable Effects: The study is powered (G*Power 80%) to answer Aim #1 for a moderate effect size (Cohen's d≥0.5), based on a Wilcoxon signed-rank test (matched pairs; one-tailed; alpha=0.05). Dmochowski et al. demonstrated a BOLD increase as high as 31% (dlPFC) within a single t-PBM session and in healthy subjects (pre- and post-t-PBM; Cohen's d=0.374). In our current design, we will compare NIR versus sham (also within a t-PBM session) in 20 subjects with impulsivity due to BD, therefore we anticipate a larger effect size.

10. Monitoring and Quality Assurance

At enrollment, each subject will be assigned a unique ID number that will be used in place of a subject's name across all study forms and documents. Documents will be stored separately from other materials in a locked filing cabinet that is only accessible by study staff. Subjects may request that their data be withdrawn by contacting Dr. Cassano (contact information provided on the consent form). Experienced, doctoral-level clinicians will be available to participants by phone, or in-person if necessary, to discuss any concerns throughout the study. This will be clearly communicated orally and in writing to subjects.

The data gathered from the project will include imaging and treatment data. Information relating to the data derived from this study will be made available to Partners IRB. The information collected in the study will be used only for research purposes. There are no plans to share any of the collected data with anyone outside of the immediate study staff.

Paolo Cassano, MD, PhD (Neuropsychiatry), Director of Photobiomodulation at MGH Depression Program and at MGH Neuropsychiatry will provide his expertise on t-PBM and its effects on psychiatric conditions. Joan Camprodon, MD, MPH is Chief of the Division of Neuropsychiatry at MGH and directs the Laboratory of Neuropsychiatry and Neuromodulation. His will provide his expertise in imaging studies of neuromodulation. Kristen Ellard, PhD Is the director of Dimensional Neuroimaging Research within the Division of Neuropsychiatry and will provide her expertise in bipolar disorder and neuroimaging. Dr. Cassano, Dr. Camprodon, and Dr. Ellard all have extensive clinical research and data safety monitoring experience. Dr. Cassano, as the principal investigator, will discuss safety concerns with research study team (CRCs and post-doc) and bring any concerns to the other co-Is, if needed. Dr. Camprodon will provide safety monitoring and insight for neuroimaging and Dr. Ellard will provide her insight for safety of bipolar disorder subjects. In addition to these internal monitors, Dan Iosifescu, MD, MSc., will serve as the independent monitor for the study. He is the Director of Clinical Research at the Nathan Kline Institute in New York and has extensive experience within the field of Psychiatry and t-PBM as a PI and co-I of many studies within the field. He will review the annual reports for safety, and findings, and he will provide feedback on the study.

Study staff will meet on a weekly basis for the duration of the study to review the progress of the study, discuss safety concerns that arise, and make recommendations to improve safety procedures if indicated. Study staff will also review and monitor data on a weekly basis to ensure adherence to protocol and accurate data collection.

Subjects will be thoroughly screened prior to starting any study procedures to ensure they meet inclusion criteria and that they have the capacity for voluntary, informed consent.

If the subject experiences any adverse event or discomfort throughout the t-PBM sessions that are not able to be alleviated by the PI or study staff, then the application session will be stopped.

An adverse event means any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice).

A serious adverse event means any event temporally associated with the subject's participation in research that meets any of the following criteria:

- results in death.
- is life threatening (places the subject at immediate risk of death from the event as it occurred).
- requires inpatient hospitalization or prolongation of existing hospitalization.
- results in a persistent or significant disability/incapacity.
- results in a congenital anomaly/birth defect; or
- any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Expected adverse events and expected serious adverse events will not be accepted by the Mass General IRB nor will they be reported unless the sponsor or investigator deems the event to be unexpected in nature. Only Unanticipated Problem Involving Risks to Subjects or Others (UPIRTSO) and Unanticipated Adverse Device Effect (UADE) Events meeting either of these definitions are considered "Unanticipated Problems" and should be reported if they occur during the conduct of the study, after study completion, or after subject withdrawal or completion. Events meeting these definitions include unexpected or unanticipated drug or device adverse reactions attributable to the intervention and that place subjects at increased risk of harm.

In the case of an unexpected adverse event and in accordance with Partners Human Research Committee Adverse Event Reporting guidelines, the PI and study staff will complete the appropriate adverse event form and send it to the IRB within the required time frame for reporting. This documentation will be completed and submitted on Insight within 5 business/7

calendar days from the day the investigator first became aware of the event. This report will include:

- a detailed description of the event
- the basis for determining that the event is unexpected in nature, severity, or frequency
- the basis for determining that the event is related or possibly related to the research procedures
- the basis for determining that the research places subjects at an increased risk of harm)
- whether any changes to the research or other corrective actions are warranted.

Experienced, doctoral-level clinicians will be available to participants by phone, or in-person if necessary, to discuss any concerns throughout the study. This will be clearly communicated orally and in writing to subjects.

All monitoring and quality assurance procedures will be in accordance with the MGH sub-committee on human studies. The PI will oversee the collection, maintenance, and analysis of the data. Research affairs will be contacted immediately in the case of unexpected adverse events likely related to the intervention. If an unexpected adverse event or serious adverse event does occur, the investigator will consider whether corrective actions should be made to study procedures in order to protect the safety and welfare of study subjects. If any changes are made the Protocol and Informed Consent Form will be updated and these edits will be submitted as an Amendment to the IRB.

If a subject's clinical condition deteriorates substantially by self-report and clinician assessment, the subject will be withdrawn from the study. Subjects may also be withdrawn if the PI feels that the study poses a substantial risk to the participant or if the PI decides that a higher level of care is needed.

Procedures used in this study are consistent with safe and ethical research practices and do not unnecessarily expose subjects to risk. Adverse events are expected to be infrequent given the excellent safety profile of t-PBM, but should they arise, the PI will review the adverse event and report it to the IRB. Moreover, study staff and subjects may report concerns directly to the IRB.

Every effort will be made to enhance the comfort of subjects while throughout the study procedures. Subjects will be informed that they can stop any study procedure at any time if needed.

11. Privacy and Confidentiality

- ☒ Study procedures will be conducted in a private setting
- ☒ Only data and/or specimens necessary for the conduct of the study will be collected
- ☒ Data collected (paper and/or electronic) will be maintained in a secure location with appropriate protections such as password protection, encryption, physical security measures (locked files/areas)

- ☐ Specimens collected will be maintained in a secure location with appropriate protections (e.g. locked storage spaces, laboratory areas)
- ☒ Data and specimens will only be shared with individuals who are members of the IRB-approved research team or approved for sharing as described in this IRB protocol
- ☐ Data and/or specimens requiring transportation from one location or electronic space to another will be transported only in a secure manner (e.g. encrypted files, password protection, using chain-of-custody procedures, etc.)
- ☒ All electronic communication with participants will comply with Mass General Brigham secure communication policies
- ☒ Identifiers will be coded or removed as soon as feasible and access to files linking identifiers with coded data or specimens will be limited to the minimal necessary members of the research team required to conduct the research
- ☒ All staff are trained on and will follow the Mass General Brigham policies and procedures for maintaining appropriate confidentiality of research data and specimens
- ☒ The PI will ensure that all staff implement and follow any Research Information Service Office (RISO) requirements for this research
- ☐ Additional privacy and/or confidentiality protections

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