Study Protocol:

Transcranial Photobiomodulation Therapy for the Treatment of Autistic Traits in Children and Adolescents with Attention Deficit Hyperactivity Disorder

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LIST OF ABBREVIATIONS

CBCL = Child Behavior Checklist
ALA = 5-aminolevulinic acid
ASD = Autism Spectrum Disorder
DHD-SC = Attention Deficit Hyperactivity Disorder Symptom Checklist
ATP = adenosine triphosphate
AVM = Arteriovenous Malformation
BRIEF-P = Behavior Rating Inventory of Executive Function-Parent Version
CTAE = Clinician-Rated Treatment Emergent Adverse Events Log
CGI-I = Clinical Global Impressions - Improvement
CGI-S = Clinical Global Impressions – Severity
DNA = deoxyribonucleic acid
EEG = Electroencephalogram
EP = Endpoint
FDA = Food and Drug Administration
FU = Follow Up
GAF = Global Assessment of Functioning Scale
IR = Infrared
HIPAA = Health Insurance Privacy Accountability Act
HIPPA = Health Information Privacy and Portability Act
LED = Light Emitting Diode
MDD = Major Depressive Disorder
MGH = Massachusetts General Hospital
MGH-SECS-C = MGH Social-Emotional Competence Scale-Clinician Rated
MGH-SECS-I = MGH Social-Emotional Competence Scale-Informant Rated
MP = Midpoint
OSHA = Occupational Safety and Health Administration
PI = Principal Investigator at the site
RM = Regression Model
Screen = Screening
SD = Standard Deviation
SRS-2 = Social Responsiveness Scale-Second Edition
SSRI = selective serotonin reuptake inhibitor
tPBM = Transcranial Photobiomodulation
TSRQ = tPBM Self-Report Questionnaire
W1 = Week 1
W2 = Week 2
W3 = Week 3
W4 = Week 4
W6 = Week 6
W8 = Week 8
W10 = Week 10

I. BACKGROUND AND SIGNIFICANCE

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by variable presentation of difficulties with socialization, reciprocal communication, and restrictive/repetitive behaviors (1). An increasingly higher prevalence of ASD is documented in each successive epidemiological survey and the disorder is now estimated to affect up to 2% of youth in the general population (2). This rise in prevalence is in part attributed to improved recognition of autism in intellectually capable populations (3).

There exists no established pharmacological treatment for the core features of ASD. Current practice consists of well-established evidence-based pharmacotherapies that are available for the management of comorbid psychiatric disorders, in order to improve quality of life and reduce symptom severity in ASD (4). Clinical trials of available treatment options reveal that compared to general population, individuals with ASD may be more susceptible to adverse effects of medications which could be dose-related, and may have lower adherence to treatment (5-8). New treatments for core deficits in ASD are needed; an intervention requiring no medication may offer better compliance and tolerability.

Attention Deficit/Hyperactivity Disorder (ADHD) is the most common psychiatric disorder recognized in youth and adults with ASD, and greatly adds to their morbidity and dysfunction, particularly in those with intact intellectual capacity (4, 9, 10). The prevalence of ADHD in the general population of school-age children is approximately 3% to 5%, although some reports show even higher incidence (11). Nearly two-thirds of referred populations of youth (ranging from 59-83%) and adults (ranging from 37-68%) with ASD suffer from ADHD (4, 9, 10, 12-17).

Both ADHD and ASD have strong shared heritable components according to the evidence from twin and family studies (3, 18-23). Up to 15% of youth with ADHD suffer from ASD and experience greater morbidity and dysfunction (24, 25). This confounding effect of ASD seems to be symptom dependent and not contingent upon reaching full diagnostic threshold (25). In fact, up to a third of ADHD youth without ASD diagnosis still struggle with persistent symptoms of ASD (henceforth termed autistic traits [ATs]) and associated compromised outcomes (26). Presence of ATs is associated with a more complicated course of ADHD, characterized as increased comorbid psychopathology, more impaired interpersonal, school, family, and cognitive functioning. Anti-ADHD medications effectively mitigate core symptoms of ADHD, but offer no improvement in the ATs. Youth with ADHD continue to suffer from the impairments associated with ATs that prognosticate a compromised course in multiple domains of functioning despite effective treatment of ADHD (26). Treating comorbid ATs in patients with ADHD could prevent functional deterioration, and improve long term outcomes. As yet, there exists no known treatment for the core features of ASD or ATs.

A novel treatment approach for social and cognitive deficits is based on transcranial application of Light Emitting Diode (LED), an invisible, non-ionizing electromagnetic wave. Referred to as *Transcranial Photobiomodulation*, tPBM consists of exposing bilaterally the frontal brain to a non-ionizing electromagnetic wave. The tPBM is invisible, penetrates the skin and skull into brain tissue, is non-invasive, and minimally dissipated as thermal energy (27). The benefits of tPBM are wavelength specific. A mitochondrial enzyme, the *cytochrome c oxidase*, is the primary chromophore for the tPBM at wavelengths of 830-850 nm (28). What follows is, increased adenosine triphosphate (ATP) production, through the respiratory chain. Ultimately,

the increased ATP leads to increased energy metabolism for the cell, and it is hypothesized that a signaling cascade is also activated promoting cellular plasticity and cytoprotection (28).

Unique properties of the tPBM have led to novel therapeutic applications in neurology, for treatment following acute ischemic stroke subjects, and in dermatology for treatment of alopecia (29-31). In psychiatric care, tPBM has been shown to be safe, effective and well tolerated compared the sham treatment in patients with Major Depressive Disorder (MDD) (32, 33).

These properties of the tPBM have led to novel therapeutic applications in neurology. In acute ischemic stroke subjects, acute treatment with the tPBM led to significantly better outcome as compared to sham (29). These results were confirmed in a different cohort of stroke patients with mild to moderate severity of illness (31). Both studies on stroke subjects showed no significant difference in rate of adverse events, as well as serious adverse events, between the tPBM and sham treated subjects (29, 31). The tPBM has also been used as a treatment of alopecia (30) and in animal models for methanol-induced retinal toxicity (28). The tPBM is already widely used for non-invasive assessment of brain function (replacing fMRI in studies of infants and young adults, under the name of Near Infrared Spectroscopy) underscoring the relatively low risk of tPBM.

Proposed treatment with tPBM has been previously studied in patients with Major Depressive Disorder (MDD) (32). MDD has been associated with deficits in brain bioenergetic metabolism. In an experimental model of depression, the mitochondrial respiratory chain (the cellular site for energy production) was found to be inhibited by chronic stress (34). Depressed subjects have also significantly lower production of ATP (an energy vector) in their muscle tissue and greater incidence of deletions in their mitochondrial DNA (35). Data from magnetic resonance spectroscopy in subjects with MDD showed that response to the augmentation of a selective serotonin reuptake inhibitor (SSRI) with triiodothyronine (a thyroid hormone) is associated with restoration of the levels of ATP in the brain (36). A preliminary open study in 10 depressed subjects has shown that the tPBM was safe, effective and well tolerated (33).

More recently, we conducted a proof of concept study with tPBM, in an open label, prospective design with 10 patients with a diagnosis of ASD between ages 18 and 55. Five patients met the rigorous responder criteria, and a statistically significant improvement was observed in all clinician and patient rated measures at midpoint and endpoint. Efficacy measures revealed that tPBM substantially improved ATs in 7 patients (70%), and was well tolerated with no treatment-limiting side-effects or serious adverse events. Adherence rate among participants was 98%.

These findings suggest that tPBM may be a promising treatment for core social deficits associated with ASD and is a safe, feasible treatment approach. The major risk of tPBM when using a laser as the light source is associated with accidental retinal exposure, when beams are projected through the lens, with increased risk of macular degeneration (37). LED light does not share the same risk level as laser light sources. Based on these promising results, this novel treatment approach is safe, well-tolerated and associated with statistically and clinically significant improvements in symptoms of ASD. We hypothesize that tPBM will be safe and effective in the treatment of ATs in youth with ADHD, and will improve social functioning, which stimulants do not address.

Aforementioned proof-of-concept study was blessed with a fast pace of recruitment, with 10 participants over a period of 18 months, despite its demanding nature for our patients. Even faster and more efficient recruitment along with a less demanding schedule for our patients is

possible. Telemedicine substitutes for face-to-face office visits through a remote, two-way video-conference through secure Internet access. Telemedicine use in the clinical setting has successfully provided specialist advice with favorable patient outcomes, satisfaction, and costs (38-41). Clinical trials are the gold standard for evaluating new therapeutic opportunities in medicine, efforts aimed at improving their efficiency are needed to facilitate patient participation in a manner that reduces dropout, and Telemedicine may offer such opportunity.

We propose an open label trial to assess the safety and efficacy of tPBM in improving ATs in ADHD youth with comorbid ATs. Eligible participants will be youth with adequately treated ADHD who present with comorbid ATs of at least moderate severity. Participants will receive tPBM daily for 8 weeks. Participants who meet eligibility criteria will be mailed the tPBM device. They will be able to administer the treatment in the comfort of home, at scheduled intervals. Accurate application of tPBM, its safety, and efficacy will be assessed during regular scheduled meetings with study clinician. These meetings will all be conducted via telemedicine with HIPAA compliant communication technology. Safety of and treatment response to tPBM will be monitored by parent- and clinician-rated measures during regularly scheduled visits. Our study will address the question whether tPBM is effective for the treatment of ATs in youth with ADHD, and whether it is acceptable among our patients.

Certain aspects of tPBM render it a feasible intervention. It can be delivered at home. It does not require ingestion of any substances. It is possible that the exposure to tPBM might be more acceptable than use of medications among some minority groups. This intervention does not require providers with specific cultural expertise or second language proficiency.

The tPBM treatment can be completed in the comfort of participants' homes, while monitoring their safety and response during scheduled medicine visits. The advantage of the tPBM treatment approach compared to pharmacotherapy is that adherence can be easily monitored. Our study will answer whether tPBM has an effect on ASD symptoms in ADHD and whether it is acceptable among our patients, for whom frequent visits otherwise would be prohibitive or render it inaccessible. As such, we propose the inclusion of a telemedicine visits in this study protocol.

II. SPECIFIC AIMS

The purpose of this 10-week open-label clinical study is to assess the tolerability, safety, and efficacy of Transcranial LED Therapy in youth patients with ADHD diagnosis who also present with at least moderate level of ATs.

Primary Objective:

- To assess the *efficacy* of tPBM for the treatment of ATs in youth with ADHD.
- To assess the *safety and tolerability* of tPBM for treatment of ATs in youth with ADHD

Secondary Objective:

- To evaluate the efficacy of tPBM in treatment of ADHD with ATs

Rationale for use of this device in patients with ASD:

Different devices have been used in study of near-infrared radiation (NIR) treatment effects in humans. We decided to use a new device, manufactured by Niraxx for its ease of application,

with safeguards to pose no risk of exposure to LED light. The device is designed as a simple headband, a common garment during most sports or leisure activities

III. SUBJECT SELECTION

Inclusion Criteria

- Male or female participants between 9 and 17 years of age (inclusive)
- Participant fulfills DSM-5 diagnostic criteria for ADHD as established by the clinical diagnostic interview.
- Participants with at least moderate severity of ASD symptoms as demonstrated by SRS raw score ≥ 75 or CGI-AT severity score ≥ 4
- Participants must understand the nature of the study. Participants must sign an IRB-approved informed consent form before initiation of any study procedures.
- Participants are willing and able to cooperate with all tests, examinations and demonstrate ability to appropriately administer the study treatment required by the protocol.
- Participants must have access to a computer with camera and broadband internet connection
- Participants have access to Apple IOS in their household.

Exclusion Criteria

Subjects will be excluded from the study for **any** of the following reasons:

- Impaired intellectual capacity (clinically determined)
- Serious chronic medical or psychiatric condition that, in the investigator's opinion, puts the subject at risk
- The subject has a significant skin condition at the procedure sites (i.e., hemangioma, scleroderma, psoriasis, rash, open wound or tattoo)
- The subject has an implant of any kind in the head (e.g. stent, clipped aneurysm, embolised AVM, implantable shunt – Hakim valve)
- Any use of light-activated drugs (photodynamic therapy) within 14 days prior to study enrollment
    - Visudine (verteporfin) – for age related macular degeneration
    - Aminolevulinic Acid- for actinic keratoses
    - Photofrin (porfimer sodium) – for esophageal cancer, non-small cell lung cancer
    - Levulan Kerastick (aminolevulinic acid HCl) – for actinic keratosis
    - 5-aminolevulinic acid (ALA)- for non-melanoma skin cancer
- The subject has any clinically unstable psychiatric conditions, is judged to be at serious suicidal risk, is determined by a clinician to have increased risk for suicidality due to medication washout, or if the clinician is concerned about washout of the light-activated drugs.
- Current treatment with a psychotropic medication on a dose that has not been stable for at least 4 weeks prior to initiating study treatment.
- Pregnant or nursing females
- Investigator and his/her immediate family

Study Population

The subject population for this study will consist of 90 subjects between the ages of 9 and 17 (inclusive), of any ethnic background, diagnosed with ADHD and presents with ATs of at least moderate severity. We will recruit subjects both internally and externally. Participants will be recruited from the pool of existing patients and new referrals to the Pediatric Psychopharmacology program and the Alan and Lorraine Bressler Clinical and Research Program for Autism Spectrum Disorders at MGH.

The Alan and Lorraine Bressler Clinical and Research Program for Autism Spectrum Disorder is a specialized ambulatory care program devoted to the assessment and treatment of individuals of all ages with ASD. It is one of only a few programs in the New England area to offer comprehensive assessment for individuals with ASD, including a complete psychiatric evaluation, psychopharmacological, neuropsychological, behavioral, and social services consultation, psycho-educational support and cognitive/behavioral therapies. The ambulatory care team consists of board-certified psychiatrists specialized in the assessment and management of ASD.

If any clinician or provider ascertains that their patient may qualify for the study and has an interest in study participation, the clinician will offer contact information for the study coordinator to the patient. The patient can then contact the study coordinator for more information on the trial. The clinician will also give the coordinator the contact information of the interested patient to the study coordinator, with the interested patient's permission. All subjects that enter the study will undergo standard screening and diagnostic procedures. Clinical records are not scanned in order to recruit subjects. Patients who potentially meet criteria for the study will only be contacted by their treating clinician and referred should the patient decide they wish to participate. Some participants (ie: subjects who express interest in participating via Rally) may not be contacted by their treating clinician regarding study participation. If a patient of an investigator decides to enroll in the trial, the process of informed consent will be conducted with a co-investigator who does not treat the patient in a clinical setting. Under no circumstances will a physician investigator obtain informed consent from his or her own patient.

IV. SUBJECT ENROLLMENT

Individuals who express interest in the study, will be screened for eligibility by the study coordinator or a research assistant via phone. If their answers to the IRB approved phone screen indicate that they may be eligible for the study, the parent/guardian will be asked to complete the Social Responsiveness Scale – Second Edition (SRS-2) online via RedCap, a secure online data capture system. The study coordinator will send a link to complete the SRS-2 electronically to the parent/guardian via REDCap. An online consent statement will appear, prompting parents to indicate their agreement to participate in the online questionnaire portion of the study. If the parent/guardian indicates their agreement, the data capture system will proceed to the SRS-2. After completing the SRS-2, eligible participants based on inclusion and exclusion criteria will either be scheduled to speak with a study clinician via phone to obtain informed consent (and assent as necessary) prior to completing further screening and baseline study procedures via virtual visit.

Study staff will send the consent form and assent form (when applicable) to subjects in PDF form ready for Adobe eSignature via email with a brief statement (email template submitted) explaining why they are receiving this form and further instructions. Study staff will schedule a time for the subject and their parent(s)/guardian to meet with a study clinician via phone or secure Zoom video call to complete the consent. The study clinician will have a conversation with the subject and their parent(s)/guardian to obtain consent in the usual fashion: review the consent form, review the inclusion and exclusion criteria, review risks and benefits of the study, review alternatives to participation, and answer any questions subjects and their parent(s)/guardian may have. If the subject and their parent(s)/guardian decide to participate, they will sign the consent form and assent form (when applicable) using Adobe eSignature. The study clinician will also sign the consent form using Adobe eSignature prior to beginning any study procedures. Subjects will be sent a copy of the signed form by email for their records.

Informed consent will be obtained prior to the performance of any protocol procedures and prior to subjects receiving the study treatment. The informed consent and assent documents will be used to explain in simple terms the risks and benefits of study participation to the subject and/or their parent/guardian. The nature of the study will be fully explained to the subject and/or their parent/guardian by a board-certified physician who is either the primary investigator or co-investigator. The subject and/or their parent/guardian will be encouraged to ask questions pertaining to their participation in the study and the subject and/or their parent/guardian may take as much time as they feel necessary to consider their participation in the study as well as consult with family members or their physician. Participation in this study is voluntary and the subjects and/or their parent/guardian may withdraw from the study at any time.

The IRB-approved informed consent documents will be signed and dated by the subject and the physician obtaining consent via Adobe eSignature. Subjects ages 14-17 will sign the same consent form as the parent, while subjects ages 9-13 will sign a separate assent form. If a subject turns 18 years old during the course of this study, he/she will be asked to sign the consent form again as an adult before continuing with the study. If the subject refuses to provide electronic consent after attaining majority status, he/she will be discontinued from the study.

The subject will meet all the inclusion criteria, have none of the exclusion criteria, and will provide their electronic signature on the Informed Consent and Assent documents (when applicable) to participate in this clinical study. Any subject that signs Informed Consent will be considered enrolled into the study, although they may not participate if they do not qualify for the study. In the event that a subject's or parent/guardian's ability to comprehend and communicate is compromised (per assessment of the Investigator), local regulations pertaining to Informed Consent signatures should be followed.

Some subjects may be recruited from among the investigator's own patients. In this case, the investigator will reinforce that participation is voluntary and the decision not to participate will not affect their care, now or in the future. Study staff will be available to contact if potential subjects have any further questions about the study and consent. Additionally, all subjects recruited from among the investigator's own patients will be offered the opportunity to discuss participation with a physician colleague before deciding whether or not to participate.

Subjects who have completed a previous medication trial in our program may be eligible to participate in this study, as described in the Study Design section. Other medical records on a subject will not be used at any point during this study.

Participation in this study is voluntary and subjects may withdraw from the study at any time. The IRB-approved informed consent documents will be e-signed and dated by the subject and the physician obtaining consent.

Enrollment of Female Subjects of Childbearing Potential

Female subjects of childbearing potential must consent (without any element of coercion) to use a double-barrier method for birth control (e.g. condoms with spermicide) if sexually active.

V. STUDY PROCEDURES

Devices and Dosing

Each subject will receive daily tPBM treatments for 8 weeks.

The probes delivering the LED light are embedded on the inside of a headband and are activated by a button press on a specific phone application, once accurate placement is ensured. Energy is administered with a radiation wavelength of 850 nm. The duration of irradiation is started at 10 min per day for the first week (days 1-7), increased to 20 min per day during the second week of treatment (days 7-14) and to 30 min per day at week 3 (days 14-21) of treatment. The dose will be escalated to 30 min daily as tolerated, if side-effects prevent increase (or if treatment response already occurred), a lower dose will be kept in order to ensure good tolerability and treatment adherence. At day 21, the clinician will recommend 40 min daily if no improvement in the context of good tolerability (Table II). Therefore, the duration of irradiation is 10-40 minutes at each application site (all sites are irradiated at the same time which is equivalent to 10-40 minutes of total time). tPBM treatment instructions will be given to patient by licensed physician (i.e. MDs) or study staff. All staff who deliver instructions must pass training that is approved by the MGH Laser Safety Committee.

There will be 10 Niraxx treatment devices to allow up to 10 subjects simultaneously receiving treatment at any given time. The treatment will be bilateral and applied to the frontal areas with application sites on the left side and on the right side [left and right forehead centered on EEG sites on F3, Fp1 and F4, Fp2 and Fz, Fpz]. Energy is administered with a radiation wavelength of 850 nm. The duration of irradiation is 10-40 minutes at each application site (all sites are irradiated at the same time which is equivalent to 10-40 minutes of total time). Each subject will receive specific instructions on appropriate application of tPBM treatment device at the screening visit. All staff who deliver instructions must pass training that is approved by the MGH Laser Safety Committee. The treatment will follow these specifications: tPBM (IR) irradiance of 18 mW/cm2; each treatment window area is 55 cm2; tPBM (IR) fluence of up to 43 Joules/cm2; energy delivered per session per device up to 2.4 kJ.

Study Design

This study is a 10-week, open-label, single treatment group designed to investigate efficacy, safety and tolerability of tPBM in treatment of ATs in youth with ADHD. The study may take up to 14 weeks from enrollment (allowing up to 4 weeks to schedule and complete initial screening and baseline visit).

If a potential subject's clinician ascertains that the patient has an interest in study participation, the clinician will offer contact information for the study to the patient and/or their parent/guardian. The patient and/or their parent/guardian can then contact the study coordinator for more information on the study. If the patient's physician is a member of study staff, the patient and his/her family will also be offered the opportunity to speak with another study physician who is not their treating clinician to review study details and consider participation. Clinical records are not scanned in order to recruit subjects.

After providing written informed consent, all subjects will complete a clinical diagnostic interview via a virtual visit with a board-certified study clinician to assess eligibility. A study clinician will complete the Reproductive Potential Form. All subject's parent/guardian will be administered an assessment battery including a brief demographic interview and the SRS-2.

If an additional family member of the subject is available, we will ask that family member to independently complete an SRS-2 form. Both forms will be scored and the form with the higher score will be used to determine subject eligibility in order to reduce the possibility of under-recognition of social impairment.

Study clinicians will complete a chart note at Weeks 0, 1, 2, 3, 4, 6, and 8. For a complete schedule of assessments, please refer to Table 1. The screening process may take place over multiple days, as necessary.

All data will be collected and entered into Research Electronic Data Capture (REDCap), an electronic data capture system that streamlines data collection and ensures data integrity. REDCap software allows researchers to design and implement study surveys electronically for collecting, storing, retrieving and manipulating data.

Subject, parent/guardian and research staff will enter survey responses into the electronic assessment forms on REDCap. A member of study staff will send the forms for the parent/guardian to fill out via REDCap. The responses will be then transmitted securely via an encrypted connection and stored in a secured database. Electronic data capture eliminates the need for subsequent data entry by staff, this minimizing human error. However, in the event that REDCap is unavailable or malfunctioning, study staff will print all study instruments and mail them to subjects and parent/guardian, thus study data will be collected in paper form.

Subjects will be instructed to administer daily tPBM treatments for 8 weeks. Each subject will be mailed a device to keep at home during study participation and return to study staff upon completion.

Concomitant Medications/Treatments

As part of the initial psychiatric evaluation, a detailed history of past and present treatments (pharmacological and non-pharmacological) will be obtained. At each study visit, subjects will be assessed for the use of concomitant medication. The guidelines for use of concomitant medications/treatments during the study are as follows:

- Participants may continue treatment with concomitant psychotropic medications (provided no exclusion criteria are met) and must remain on a stable dose during the course of the trial.
- Subjects requiring initiation of acute or chronic medication treatment may be discontinued from the study if treatment is judged by the investigator to interfere with the assessment of study drug effect.

- Non-pharmacological treatments such as supportive individual, family, or group therapy will be permitted provided they were in place for a substantial period of time (>1 month) prior to study enrollment and remain unchanged during the course of the trial.
- No new non-pharmacological treatments may be initiated during the course of the trial.

Washout Period

After the screening period, subjects who are currently taking any light-activated drugs, as noted in exclusion criteria, and willing to discontinue the use of their medication may do so in order to be eligible for participation in this study, if clinically appropriate per clinician judgment. Subjects will not be asked to discontinue their medication if it poses an increased risk for suicidality. If appropriate, medication washout will be recommended by our clinicians to participants and current providers. Medication washout will not occur without approval from the prescribing clinician. Clinician's will determine a washout schedule based on the half-life of the medication, the adverse effects associated with treatment and withdrawal, and an assessment of individual factors including duration on drug and dose. No subjects will be asked to discontinue ongoing exclusionary medications to participate in the study; however, if the subject is already tapering the medication off for clinical reasons at the time of screening and evaluation for participation, they will be considered eligible to participate only after the washout period as described. Our office does not take over care for the patient, but remains available during this time period. The washout schedule will be discussed with the participant and current providers.

Flexible Titration Schedule

Titration of tPBM will follow a flexible titration schedule with an option for slower titration, holding at lower dose, or lowering the dose based on tolerability and response to the tPBM as per clinician judgment. Dose will be adjusted upward per the flexible titration schedule provided the treatment is well tolerated. For the detailed titration schedule, please refer to Table II.

Subject Confidentiality

Any information and data collected during any subject's participation in this investigation will be considered confidential. The Investigator will need to ensure that all subjects' anonymity will be maintained on all documentation by completely redacting (eliminating or "blacking out") each subject's name and/or other identifying information. The identifying information will be replaced with the subject's study number. For the purpose of internal monitoring, Niraxx Inc. will use participants' email addresses to access treatment adherence and compliance data, which will be sent directly to the study team on a weekly basis via secure email and stored on a secure server at MGH. To protect subject confidentiality, Niraxx Inc. follows the General Data Protection Regulation (GDPR)— a European Union data protection and privacy regulation (42). Further, Niraxx Inc. will only be provided the email addresses of subjects' who provided their consent to allow Niraxx to access treatment adherence data. With the exception of providing email addresses to Niraxx Inc. for the purpose of monitoring treatment adherence, the investigational staff is not to provide to Niraxx Inc. information such as subject's telephone numbers, home address, personal identification numbers such as passport numbers, etc. Care must be taken by investigational staff when communicating with representatives from Niraxx Inc. in the form of telephone or electronic correspondence in not providing information (except for the email addresses of consenting subjects) that may disclose a subject's identity.

Documents associated with the study that are not intended to be submitted to Niraxx Inc (e.g., signed Informed Consent Forms) must be kept in strict confidence by the Investigator. Only study personnel and regulatory authority inspectors will have access to these confidential files.

1.1. Study Visits

Study visits will occur entirely via TeleHealth or Zoom, which is maintained by Partners HealthCare. In the event that TeleHealth or Zoom malfunction or a subject loses access to a device compatible with these platforms at scheduled time, the study visit will be rescheduled. The study involves screening, baseline, and a series of clinical monitoring and follow up visits.

Screening Process (Week 99)

The screening process includes the following components:

- Subjects will virtually meet with a study clinician for a psychiatric evaluation and review of medical history.
- The study clinician will ask the participant about his or her symptoms of autism spectrum disorder.
- The study clinician will ask the participant about his or her symptoms of ADHD.
- The study clinician will ask the participant and their parent/guardian questions regarding their child's reproductive potential. If deemed necessary, female participants of childbearing potential will complete a urine pregnancy test. If a participant has a positive pregnancy test, she will not be able to take part in the study. The study doctor will inform the participant and discuss the clinically appropriate course of action. The participant will be offered 3 follow-up visits.
- We will ask the participant's parent/guardian complete three observer-rated questionnaires about their child's ASD symptoms (SRS-2, CBCL, MGH-SECS). These questionnaires will take approximately 30-40 minutes to complete.
- We will ask the participant's parent/guardian to complete a brief demographic interview collecting information regarding socioeconomic status and history of head injury or trauma. This will take about 5-10 minutes to complete.
- Optional: if an additional parent/caregiver is available, we will ask them to complete one to three observer-rated measures on REDCAP.

We anticipate that subjects may enter this trial following completion of/withdrawal from other protocols in our office, and that there may be procedural overlap. So as to not burden subjects/parents/guardians with redundant time commitments, we will use the following diagnostic data previously collected: If a subject has completed an evaluation with one of the study clinicians in the three years preceding their entrance to the study, they will not be asked to repeat these overlapping diagnostic procedures. We will use the study diagnostic data previously collected so as to not burden the subject with redundant time commitments. However, the study clinician will review the interval time period to assess for clinically significant medical or psychiatric history to ensure that the subject meets appropriate study entrance criteria.

Study participants and/or their legal guardians may request the results of their cognitive testing. In this case, the subject will receive a letter providing a basic interpretation of the results and referring them to the department's supervising neuropsychologist for any questions or concerns.

The following assessments will be performed at the Screening Visit:

- CGIs
- GAF
- CTAE
- Concomitant Medications
- Demographic Interview
- SRS-2 (Pre-Screening)
- CBCL
- MGH-SECS-I
- MGH-SECS-C
- BRIEF-P

Study Treatment Phase (Weeks 0-8)

Pregnancy potential will be monitored at screening, baseline, Week 2, Week 4, and Week 6 by a clinician-rated reproductive potential form. If, during any of these visits the participant is deemed to have pregnancy potential, a member of study staff will contact the participant and their parent/guardian to complete a phone screen to ensure the participant and their parent/guardian understand why a urine pregnancy test is necessary, explain the required procedures, and obtain verbal consent from both the parent/guardian and the subject to send the urine pregnancy test to their home address. If both the parent/guardian and the participant provide verbal consent, a pregnancy test will be overnight shipped using study funds and sent directly to the subject's home address within 24 hours. The participant will be asked to stop treatment until the urine pregnancy test is performed. In addition, a phone call will be set up at a specified time the next day. During this call, the study coordinator will review the procedure for completing the urine pregnancy test while on the phone and have the subject complete the test while remaining on the line. The subject/subject's parent or guardian will verbally report the result to the study coordinator, and will also send visual confirmation (i.e. a photo of the test with results send via secure email) prior to continuing the study treatment. If the participant and/or their parent/guardian decide that they no longer feel comfortable completing the urine pregnancy test, they will be withdrawn from the study.

The primary investigator may determine that a subject can verbally and visually report the results of the pregnancy test without their parent/guardian. This determination will be made based on clinical judgment, including the patient's report of previous illness and their reliability in reporting symptoms.

Baseline Visit (Week 0)

The overall baseline session is estimated to last about 60 minutes. The subject will be virtually examined to inspect the sites of application (left and right forehead) for any possible skin lesions (e.g. laceration or signs of inflammation) which would contraindicate the treatment. The subject will then be instructed again on the appropriate administration of tPBM.

The treatment device is classified as an "Exempt" device in accordance with the requirements of the international standard EN 62471 – Photobiological safety of lamps and lamp systems and, when used correctly, the output is less than the maximum permissible exposure (MPE) no special controls are needed for the environment it is to be used in. At the time of study implementation, the staff will be provided training on basic safety procedures relative to the use of the device. The staff will then virtually instruct the subject's parent/guardian on the administration of the tPBM such that the headband is appropriately placed. The delivery of the tPBM is expected to last 10-40 minutes total (simultaneous application on the left and right forehead). The subject will be asked to rest for five minutes after the delivery of tPBM. Sites of application will be inspected at each study visit.

Subjects will be instructed to administer the treatment sessions daily for eight weeks, with each session lasting 10-40 minutes. Subjects will be instructed to contact the investigator or a member of his staff at any time between visits concerning adverse events or worsening of symptoms.

Following assessments will be performed at the Baseline Visit:

- CGIs
- GAF
- CTAE
- Concomitant Medications
- ADHD-SC

Study Treatment: Virtual Clinical Monitoring Visits (Weeks 1-6)

There are 5 monitoring visits scheduled at Week 1, Week 2, Week 4 (Midpoint), Week 6, and Week 8.

Participants will be prescribed to administer study treatments at home daily for a period of 8 weeks. Study visits will have a visit window of +/-3 days to facilitate scheduling.

During the visits, the participants will be asked questions about the symptoms of ADHD and ATs and general health in addition to any present side effects or changes in their medications. At weeks 2, 4 (Midpoint), and 6 the participant will be asked to fill out questionnaires.

Following assessments will be performed at the Week 1, Week 2, Week 3, and Week 6 Visits:

- CGIs
- GAF
- CTAE
- Concomitant Medications
- TSRQ

Following assessments will be performed at the Midpoint (Week 4) Visit:

- CGIs
- GAF
- CTAE
- Concomitant Medications
- ADHD-SC
- SRS-2

- BRIEF-P
- TSRQ
- CBCL

1.1.1.1 Study Endpoint Visit (Week 8, or Endpoint)

At the conclusion of the endpoint visit, the subject will be asked to mail the Niraxx G1 Headband device back to the primary investigator. If requested, the subject will be provided with shipping materials.

Following assessments will be performed at the Week 8/Endpoint Visit:

- Urine Pregnancy Test (for females of childbearing potential)
- CGIs
- GAF
- CTAE
- Concomitant Medications
- MGH-SECS-C
- ADHD-SC
- SRS-2
- BRIEF-P
- TSRQ
- MGH-SECS-I
- CBCL

1.1.1. Post-Study Follow Up Visit (Follow Up, Week 10)

After Treatment completion, subjects will continue with one more clinical study visit after 2 weeks, to measure the long-term effect of tPBM. Post tPBM administration, subjects will be permitted to start or change treatment with existing or new medications, as clinically necessary (and at any time in the study if severe worsening of symptoms occurred – see 5.7. Study Discontinuation). Follow Up assessments will be carried out, including Clinician- and Patient-Rated assessments.

Following assessments will be performed at the Week 10 Visit:

- CGIs
- GAF
- CTAE
- Concomitant Medications
- SRS-2
- ADHD-SC
- TSRQ

1.2. Study Discontinuation

We will encourage subjects to continue enrollment in the study via follow-up visits regardless of the nature of discontinuation of the tPBM. At the end of the study, we will refer the subjects to their counselor and/or psychiatrist and will communicate clinical data upon signed authorization. If the CGI-S increases more than 2 points during the study, the subject will be counseled to start

or change to an FDA-approved medication treatment. If the CGI-S increases more than 5 points or if a subject becomes actively suicidal as per clinician judgment, termination from the study will be mandated. Subjects who are deemed actively suicidal and are in imminent danger will be escorted to Acute Psychiatric Service (the local psychiatric Emergency Department at Massachusetts General Hospital) for evaluation and subsequent hospitalization. If the subject is appropriate for outpatient monitoring, the subject will be followed with frequent appointments outside the study. Each subject will have the Investigator's contact information as well as instructions on how to call for emergency services, if needed.

If study participation is discontinued due to safety reasons, participants will receive three follow-up visits, while appropriate psychiatric follow up access is assured with their treating psychiatrist. If emergent suicidality were to occur during the course of the study, the supervising clinician will then directly assess the level of risk and take the appropriate action (including contacting treatment providers, working on a safety plan, arranging for emergency evaluation via an ER, calling 9-1-1, etc.). The clinician will document the actions taken, and it will be noted in the participant's file. Subjects who discontinue due to non-compliance with the protocol will receive a referral to treaters in the area.

A participant may withdraw consent at any time for any reason (e.g., lack of efficacy, adverse events, etc.). A subject may be withdrawn from the study by study staff at any time if any of the following conditions are met:

- Worsening of ATs, ADHD or current/emergent major psychiatric disorder.
- Subjects who experience intolerable adverse effects as determined by the PI.
- Emergent suicidality
- Pregnancy
- Failure to keep study appointments for more than 2 consecutive visits
- Failure to utilize the telemedicine platform
- Clinical judgment of the investigator

Subjects may receive three clinical follow-up visits at the completion of the study (or if they are required to discontinue for safety reasons), allowing adequate time for appropriate psychiatric referrals to treaters in their communities. Follow-up visits are optional and are at no cost to participants. These visits are not part of the clinical trial and no research data will be collected during follow-up. Subjects who fail to keep study appointments or are non-compliant may be dropped from the study. These study subjects will be given a referral to treaters in their area but will not be offered three follow-up visits.

If a subject would like us to forward their clinical history to his/her primary care physician, or a new clinician, we will forward any pertinent information with the proper completed release of information authorization form. If a subject who has come from the clinic of the investigator happens to drop out of the study, he or she will return to his or her treating physician.

Study Assessment Scales and Forms

Subjects will be evaluated at scheduled intervals. At each visit, measures of safety and efficacy will be obtained using assessments of psychiatric symptoms and functioning (CGIs, GAF) and measures of adverse effects (CTAE). At the Midpoint (end of week 4) and Endpoint study visits (Week 8 or Endpoint), additional clinician-, subject-, and informant-rated assessments will be repeated (see below for details).

1.2.1. Clinician-Rated Assessments

1.2.1.1. Clinician-Rated Behavioral Measures

(Administered at all visits)

- Clinical Global Impression Scale (CGI; (43)): The CGI is a measure of illness severity, improvement, and efficacy of treatment. The score for severity ranges from 1 (normal, not at all ill) to 7 (among the most extremely ill subjects). Improvement ranges from 1 (very much improved) to 7 (very much worse). The effectiveness index measures to what extent the subject is experiencing therapeutic effects in conjunction with the level of adverse events they are experiencing. CGI scales will be used for the assessment of ADHD and ATs
- Global Assessment of Functioning Scale (GAF; (44)): composite rating of an individual's overall level of functioning (1= worst to 100 = best).

(Administered at baseline and/or screening, midpoint, and endpoint)

- MGH Social-Emotional Competence Scale [Clinician-Rated Measure] (MGH-SECS-C): This is a 37-item scale that assesses change in the frequency and severity of core and associated symptoms of ASD.
- ADHD Symptom Checklist (ADHD-SC) assesses each of the individual symptoms of ADHD based on the DSM (0-3 on a scale of severity)

1.2.1.2. Clinician-Rated Safety Measures

(Administered at all visits)

- Clinician-Rated Treatment Emergent Adverse Events Log (CTAE): This form captures any adverse events (serious or otherwise) specifically related to application of the tPBM experienced during the study, along with duration, severity, cause, treatment, and outcome.
- Concomitant Medications: This form captures any additional medications taken during the study.

1.2.2. Parent-Rated Assessments

(Administered at screening evaluation)

- Demographic Interview: This brief interview will collect information regarding socioeconomic status and history of head injury or trauma (45).

1.2.2.1. Parent-Rated Behavioral Measures

(Administered at screening and/or baseline, midpoint, endpoint and follow up study visits)

- Social Responsiveness Scale-Second Edition (SRS-2; (46)): a 65-item rating scale completed by the parent used to measure the severity of autism spectrum symptoms as they occur in natural settings.
- Behavior Rating Inventory of Executive Function-Parent (BRIEF-P;(47)): a 78-item rating scale to assess level of executive function deficits.

- Child Behavior Checklist (CBCL;(48)): is a parent-report questionnaire that evaluates maladaptive behavioral and emotional problems, both internalizing and externalizing, in children ages 6-18.

(Administered at baseline and endpoint)

- MGH Social-Emotional Competence Scale [Informant-Rated] (MGH-SECS-I): This is a 37-item scale that assesses social competence and abilities on a Likert scale from 0 to 6.

1.2.2.2. Parent-Rated Safety Measures

(Administered at Study Visits 2, 4, 6, 8)

- The tPBM Self-Report Questionnaire (TSRQ) – An open-ended questionnaire focusing on potential inconveniences and discomforts related to the tPBM. It will be offered at each study visit after the beginning of tPBM treatment.

Data Collection Forms

A number of procedures are in place to assure data integrity and protocol adherence. We will use Research Electronic Data Capture (REDCap) to support direct data entry by patients and study staff. REDCap is a free, secure, HIPAA compliant web-based application hosted by the Partners HealthCare Research Computing, Enterprise Research Infrastructure & Services (ERIS) group. REDCap is an electronic data capture system that streamlines data collection and ensures data integrity. REDCap software allows researchers to design and implement study surveys electronically for collecting, storing, retrieving, and manipulating data.

Participants will be sent the data collection forms via REDCap emails. Only those subjects who receive the link via REDCap email will be able to access the questionnaires. The responses will then be transmitted securely via an encrypted connection and stored in a secured database. Electronic data capture eliminates the need for subsequent data entry by staff, thus minimizing human error. However, in the event that REDCap is malfunctioning, study staff will print all study instruments and the study data will be collected via telemedicine and recorded on paper forms.

Self-report measures will be completed by participants on a computer, directly into REDCap, thus minimizing errors due to data entry. For clinician-administered measures, all clinicians and independent evaluators (IEs) will enter responses directly in REDCap.

To minimize missing data for self-report forms, we will program missed question warnings in REDCap that will alert participants in real-time if they inadvertently skip a question. Participants may then go back and answer any missed questions, or, if they intentionally skipped questions, they may ignore the warning message and continue answer the remaining questions. We will also program real-time range checks in REDCap that generate error messages if a value outside the acceptable range is entered for a given field. To ensure confidentiality, data will be identified in the database only by subject number, visit number, and date of visit. By recording the study data in this manner, the information can be considered ‘de-identified’ and therefore compliant with the Standards for Privacy of Individually Identifiable Health Information (“Privacy Rule”) of the Health Insurance Portability Act of 1996 (HIPAA). Any data that is transmitted electronically will be fully encrypted and password protected. Subjects’ names will not be entered into the database; each will be uniquely identified only by an ID number. Consent

forms, any hard copy PHI, and any study measures that are completed on paper will be kept and filed in locked office cabinets.

VI. BIOSTATISTICAL ANALYSIS

Sample Size

The primary outcome measure for this open-label, single arm trial will be reduction in ASD symptoms as measured by change in SRS-2 total raw score from baseline to endpoint. We base our power calculations on a two-sample paired-means test. We assessed power in terms of Cohen's definition of medium and large effect sizes because they are indicative of clinically meaningful differences. These effect sizes correspond to 0.5 and 0.8 standard deviation (SD) changes form baseline to endpoint, respectively, and have been widely accepted in the fields of psychiatry and behavioral sciences. The following power calculations assume a two-tailed test, an alpha level of 0.05, a moderate strength correlation between baseline and endpoint scores (r=0.5), a standardized scale of measurement (i.e. mean of zero and standard deviation of 1.0), and a sample size of 60 subjects. We have 99.9% power to detect a large effect size (0.8 SDs) from baseline to endpoint and we can achieve adequate (80%) power to detect effect sizes as small as 0.37 SDs. Our goal is to have 60 subjects exposed to the treatment. In anticipation of a 33% attrition rate, we will need to enroll 90 subjects to ensure 60 subjects are exposed.

Considering the open-label single group design, we will rely on comparisons of the participants' performances at baseline prior to the initiation of treatment relative to their scores at the last assessment (completion/drop-visit). This design largely protects against the bias introduced by confounding factors. That is, since the same participants are tested on multiple occasions, all static confounding factors are perfectly balanced, and can have no impact on the findings. However, dynamic confounding factors may have impact on the findings (ex. Bias) and can still result from time-varying factors that are not associated with the outcomes, which is an inherent limitation of an open-label design. However, we are confident that any such factors will have a minimal impact on this study considering the duration of the trial. Since we are following subjects over a short period, missing data are not expected to impact our analyses such that standard statistical analyses will be employed. Specifically, we will employ longitudinal mixed-effects regression models (RM) with random effects for the subjects using Stata 16.0 (49). This approach has several advantages over traditional methods such as repeated measures ANOVA or MANOVA [19]. Unlike traditional methods, mixed effects RMs do not exclude subjects with missing data, can incorporate covariates (both time-varying and not) (Gibbons 1993), and can estimate the size and significance of variables predicting group outcome after accounting for individual variation in outcome. The RMs will use robust standard errors to account for the repeated measures on each subject. We will test binary data using mixed-effects logistic RMs, count data with mixed-effects Poisson RMs, and normally distributed data with mixed-effects linear RMs. Each model will predict outcome score from study visit (continuous predictor).

Primary Objective: posits that tPBM for the treatment of ATs in youth with ADHD will be safe and effective in the treatment of ATs in youth with ADHD. Our primary measure of efficacy will be the SRS-2 Total raw score which is collected at baseline, midpoint, and endpoint. The psychometric properties of the SRS have been well established as a valid measure to assess for autistic traits and can distinguish autism from other neuropsychiatric conditions (20, 50). We will examine the change in SRS-2 Total raw score over time using a mixed-effects linear RM. Our

dependent variable will be raw score on the SRS-2 Total scale and our predictor will be study visit (continuous). Secondary measures of efficacy for the treatment of ATs will be the SRS-2 subscales which include Awareness, Cognition, Communication, Social Motivation, and Restricted Interests and Repetitive Behavior. These subscales will also be analyzed using mixed-effects linear RMs predicting subscale score from study visit (continuous). Safety and tolerability will be assessed by examining adverse events reported throughout the trial.

Secondary Objective: posits that tPBM will be effective in the treatment of ADHD with ATs. The measure of efficacy for this objective will be the ADHD-SC which is collected at baseline, midpoint, and endpoint. We will examine the change in ADHD-SC score over time using a mixed-effects linear RM. Our dependent variable will be ADHD-SC score and our predictor will be the study visit (continuous).

Accountability/Investigational Product Control

U.S. federal law and ICH Guideline E6 § 5.14 requires that all investigational medical devices be strictly controlled. All study devices must be kept in a secured area at the clinical sites in compliance with all applicable FDA (U.S. sites) regulations.

The Principal Investigators or designated study site personnel who verify the receipt of the devices/device accessories must complete the Device/Accessories Acknowledgment Form and fax a copy to Niraxx, Inc. Device Accountability and Acknowledgment Logs will be maintained at study site. These logs will list all equipment received, the receiving date, the serial number of each device. Study site personnel will initial the log each time the device is used. Niraxx device use will also be recorded on the appropriate CRF.

Malfunctioning devices and device accessories, including all components, will be returned to Niraxx, Inc. for investigation, at Niraxx, Inc. expense.

VI. RISKS AND DISCOMFORTS

All adverse events will be recorded from the time of Informed Consent through study completion, or termination. The Adverse Event CRF must be completed and submitted to the IRB, as required. Regulations for adverse event handling and reporting contained in the FDA and ICH Guidelines will be adhered to.

Consideration of Adverse Events will hereafter consist of Adverse Events, Serious Adverse Events, and Adverse Device Effects, including Anticipated Adverse Device Effects and Unanticipated Adverse Device Effects.

- ***Adverse Event*** is defined as any untoward/undesirable clinical occurrence in a clinical investigation of a subject using a device and/or product and which does not necessarily have a causal relationship with this treatment. An Adverse Event can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a device product, whether or not considered related to the device product. Only abnormal laboratory values that are deemed clinically significant by the investigator will be classified as adverse events.
- ***Serious Adverse Event*** is defined as any untoward/undesirable adverse experience that results in any of the following outcomes: 1) death; 2) a life-threatening adverse

experience; 3) inpatient hospitalization or prolongation of existing hospitalization; 4) a permanent/persistent or significant disability/incapacity or a congenital anomaly/birth defect; 5) important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

- ***Anticipated Adverse Device Effect*** is defined as any adverse effect related to the device or procedure, which is identified in the protocol.
- ***Unanticipated Adverse Device Effects*** is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Potential Adverse Events

Risks to the subject may include but are not limited to the following:

The OLS emits light with a longer wavelength than the human eye can see. Since the OLS is classified as an "Exempt" device in accordance with the requirements of the international standard EN 62471 – Photobiological safety of lamps and lamp systems and, when used correctly, the output is less than the maximum permissible exposure (MPE) no special controls are needed for the environment it is to be used in. The staff will be provided training on basic safety procedures relative to the use of the device. The subject administering the tPBM will be instructed on safe application of it, specifically not to operate the Niraxx device unless it is in direct contact with the subject's skin.

Failure of the Niraxx device, resulting in the cessation of investigative therapy can cause:

1. No adverse event to our knowledge
2. Unforeseeable adverse events

Delivery of the infrared LED energy to an inappropriate site, such as directly over the open eye, is not recommended but should pose no risk to the subject:

Based on previous consumer observations, application of the Niraxx device may result in mild thermal sensation of warmth during the use. The temperature of the skin is well below the level for thermal damage.

Based on human clinical trial experience to date and sale of the device for its intended use of treating periorbital wrinkles since March 2008, each adverse event listed below has been reported by less than 0.1% of all subjects and users:

1. Application Site Erythema
2. Application Site Pain
3. Application Site Discomfort
4. Application Site Warmth
5. Application Site Reaction
6. Headache

Additional information on adverse events and prior clinical experience can be found in the User Guide. Other potential risks are described below:

Risk of Depression, Suicidality & Manic Switch: Worsening of depression and increased suicidality are possible complications of antidepressant treatments which could be prescribed to subjects with ASD and mood disorders. We will minimize this risk by selecting only subjects who do not present active suicidal ideation at screening. We will also discontinue any subject who develops active suicidal ideation during the course of the study and arrange for appropriate levels of care and standard treatment. Manic switches are possible adverse events and will be closely monitored during treatment as well. Regularly scheduled clinical study visits will allow early recognition of treatment-emergent suicidal ideation or prodromal hypomanic signs. Subjects who develop mania or hypomania will be discontinued and provided appropriate level of care.

Answering detailed questionnaires may create a mild degree of inconvenience for the subjects and will be monitored by study clinician.

Risks of Assessments/Questionnaires

Some questions may make subjects feel uncomfortable because of the nature of the question topics. Some questions ask about possibly sensitive information, including questions pertaining to alcohol and drug abuse. Subjects may refuse to respond to any questions they do not feel comfortable answering.

Adverse events and unanticipated problems will be reported to the PHRC according to current guidelines. We will follow and adhere to all guidelines as defined and outlined on the Partners Human Research Committee web site: http://healthcare.partners.org/phsirb/adverse_events.htm

Other Adverse Events Related to Study Treatment

Problems and side effects not listed above and not known at this time could occur. Subjects will be informed of any newly discovered risks as investigators come to learn of such knowledge, if applicable. At this time, there is no research that examines the long term effects of tPBM treatment. As such, the long-term effects of this treatment are unknown.

Safety Monitoring

The study subjects will undergo frequent clinical evaluations including depressive scores, concomitant medications, adverse events, and serious adverse events and unexpected device events will be recorded from study entry through completion. Additionally, doctors must monitor a subject's safety by asking the subjects frequently about the subject's own comfort during treatment application.

If skin erythema is present, treatment will be suspended. Patients will be instructed to contact the study site principal investigator or a member of his staff at any time between visits concerning adverse events or worsening of symptoms. If at any study visit the subjects' clinical condition is significantly worsened from baseline (operationalized as the clinical global impression improvement score, CGI-I, of 6 or higher) or if a subject becomes actively suicidal with intent and/or plan, based on the C-SSRS scale and/or the clinical interview, the subject will be offered to start an antidepressant medication. If the subject were deemed at imminent danger as a result of suicidality, s/he would be discontinued from the study and referred to appropriate clinical treatment (see 4.7.3 Study Discontinuation).

The Principal Investigator (Dr. Ceranoglu) will have weekly meetings which will include study RAs; during these meetings calls they will discuss all Adverse Event reports to identify any safety concern, based on such concerns they will be able to decide temporary discontinuation of study enrollment, modifications of the study protocol, or to terminate the study.

Research assistants responsible for data collection and storage will be aware of and comply with all regulatory requirements related to adverse events. In the event that a patient becomes ill or is injured as a direct result of study participation, medical care will be made available. All adverse events (and device events) will be followed to resolution and reported to the MGH IRB as serious in the event that 1. they are unanticipated and possibly related to the study (same reporting as SAE) or 2. if they meet any one of the following criteria: Any fatal event, immediately life-threatening event, permanently or substantially disabling event, event requiring or prolonging inpatient hospitalization, or any congenital anomaly. This also includes any event that a study investigator judges to impose a significant hazard, contraindication, side effect, or precaution.

Expedited review will occur for all events meeting the FDA definition of Serious Adverse Events (SAEs) – i.e., any fatal event, immediately life-threatening event, permanently or substantially disabling event, event requiring or prolonging inpatient hospitalization, or any congenital anomaly. This also includes any event that a study investigator judges to impose a significant hazard, contraindication, side effect, or precaution. For purposes of this study, all SAEs will be required to be reported to the IRB, regardless of any judgment of their relatedness to the study device. All relevant information will be reported to the IRB for each SAE including information about the event and its outcome, dosing history of all study tPBM applications, concomitant medications, the subject's medical history and current conditions, and all relevant laboratory data. Notification by e-mail of all related study forms shall be made to the IRB within 2 days of the occurrence of any SAE. Information will be reviewed and a determination made of whether there was any possible relevance to the study tPBM exposure. Additional reporting to local IRBs will be done within 5 business days/7 working days of the date the investigator first becomes aware of the problem. If at any time during the course of the study, the IRB judges that the risk to subjects outweighs the potential benefits, the IRB shall have the discretion and responsibility to recommend that the study be terminated.

Reporting Procedures for All Adverse Events

After review with the subject by the study site personnel, all Adverse Events occurring during the study, whether or not attributed to the Niraxx device or tPBM procedure, observed by the Investigator or reported by the subject, will be documented in the subject's source document and on the appropriate CRF pages. The following attributes must be assigned:

1. Description of event
2. Date of onset
3. Date of resolution (if applicable)
4. Seriousness
5. Relationship to the study device and/or procedure(s)
6. Intensity
7. Action(s) taken
8. Outcome(s)

Intensity is defined as a measure of the severity of a reaction, effect or experience. The measurement(s) are described as mild, moderate or severe. The event itself, however, may be of relative minor medical significance.

The intensity of Adverse Events is assessed as mild, moderate or severe according to the following index scale:

- ***Mild.*** The Adverse Event is transient, requires no treatment, and does not interfere with the subject's daily activity.
- ***Moderate.*** The Adverse Event introduces a low level of inconvenience or concern to the subject and may interfere with daily activities, but is usually ameliorated by simple therapeutic measures.
- ***Severe.*** The Adverse Event interrupts the subject's usual daily activity and requires systematic therapy or other treatment.

If the Adverse Event is of such intensity in the Investigator's judgment that it warrants withdrawal from the study, the subject should be withdrawn from treatment. The subject should be given appropriate care under medical supervision until symptoms resolve.

The relationship of an Adverse Event to the study device or procedure will be graded as follows:

- ***Unrelated.*** The Adverse Event is not associated with the study device use.
- ***Possible.*** This causal relationship is assigned when the Adverse Event:
    - Follows a reasonable temporal sequence from device use,
    - Could have been produced by the subject's clinical state or other modes of therapy administered to the subject, or
    - Cannot be reasonably explained by known characteristics of the subject's clinical state.
- ***Definite.*** This causal relationship is assigned when the Adverse Event:
    - Follows a reasonable temporal sequence from device use;
    - Abates upon discontinuation of the treatment; and
    - Is confirmed by the reappearance of the Adverse Event on repeat exposure.

Serious Adverse Events

All Serious Adverse Events must be reported to the overseeing Institutional Review Board (IRB), FDA, and Niraxx, Inc as required.

If the Investigators are notified by Niraxx, Inc or its designee of any Serious Adverse Events that are considered to be Unanticipated Adverse Device Effects, the Investigators must notify his/her own IRB/EC as required.

Deaths

Deaths which must be reported to Niraxx Inc include all deaths while participating the study.

Withdrawals for Adverse Events

All Adverse Events which result in the subject's withdrawal from the study must be reported immediately by telephone to Niraxx Inc.

The Investigator may be asked to provide detailed follow-up information. The Investigator will determine the reportability of the event on a case-by-case basis, and will report to the appropriate regulatory authorities evaluating the study device as necessary.

Subject Disposition Criteria

Withdrawal from the Study

Each subject and the Investigator reserve the right at any time to terminate a subject's participation in the clinical investigation.

Possible reasons for withdrawal or removal from the study may include:

- The subject voluntarily withdraws consent.
- The subject was not eligible based on the study inclusion and exclusion criteria.
- The subject develops an Adverse Event that would not allow continuation in the study.
- The subject has an Adverse Event which in the opinion of the Investigator warrants withdrawal from the study. Niraxx Inc must be notified within two business days.
- A decision is made by the subject and/or Investigator that the subject should be withdrawn from the study.
- Subject death
- Positive pregnancy test

When a subject withdraws or is removed from the study, the following will be performed, if feasible, at the study termination (exit) visit:

- Progress Note
- Virtual Examination of Exposure Sites
- MGH-SECS-C
- CGI
- GAF
- CTAE
- Concomitant medications form
- ADHD-SC
- SRS-2
- BRIEF-P
- TSRQ
- MGH-SECS-I
- CBCL

For all subjects who withdraw from the study prematurely, the date, and reason for withdrawal will be documented.

Lost to Follow-Up

If a clinical staff is unable to contact a subject or if the subject fails to appear for a visit, three documented phone calls should be made, followed by a certified letter (or its equivalent). The certified letter should detail the need for the subject to appear for a visit, the site's unsuccessful attempts to contact the subject, and that failure to contact the site will result in the subject being withdrawn from the study.

If the certified letter is returned to the site as undeliverable or the letter is delivered but the subject does not contact the site and no other contact is made with the subject or the subject's caregiver, then the subject will be considered Lost to Follow-up and discontinued from the study. All attempts to contact the subject will be documented.

VIII. POTENTIAL BENEFITS

There may be no direct benefit to subjects participating in this study. Participants may benefit by potentially experiencing improvement in ATs symptoms and by gaining knowledge about ATs.

Study subjects will receive comprehensive clinical assessment of their psychiatric condition. This information will be readily available to their counselors if the subjects agree to disclose. This information might guide counseling in the long term treatment. In the short-term, the subject will receive close and systematic monitoring, beyond current standards of care. Easy access to routine appointments are also a potential benefit in the community population, which is often underserved. The subjects will have access to a different modality of treatment if counseling was not sufficient and if medications were not acceptable to them. However, there may be no improvement at all, or benefit to participant.

IX. MONITORING AND QUALITY ASSURANCE

Consistent with good clinical practice, safety will be monitored at each study visit by a subject's assigned clinician. This clinician will be available 24 hours a day by page. The principal investigator will supervise all study activities including ratings and reported adverse events. All procedures have been designed to minimize subject discomfort, and no subject will be asked to engage in research procedures not outlined in the consent form.

If a subject is withdrawn from the study due to adverse events, lack of response, or as a decision by the clinician, they will be offered open treatment for three months, giving adequate time for appropriate psychiatric care to be arranged.

Safety will be monitored through treatment-emergent adverse events. Subjects will be monitored for adverse events at each visit. All adverse events will be recorded. A subject may be dropped from the study or dosage may be decreased at any time due to adverse events. All adverse events will be reported to the PHRC according to PHRC guidelines. All concomitant medications will be assessed at every study visit.

2. REFERENCES

3. ATTACHMENTS

3.1. Table I. Study Schema

Weeks	**99**	**0**	**1**	**2**	**3**	**4**	**6**	**8**	**10**
Visits	**Screen**	**Baseline**	**W1**	**W2**	**W3**	**MP**	**W6**	**EP**	**FU**
Informed Consent	X								
tPBM Device Subject Training	X	X							
tPBM Treatment - 10 min/day		X							
tPBM Treatment - 20 min/day			X						
tPBM Treatment - 30 min/day				X					
tPBM Treatment - 40 min/day					X	X	X	X	
Diagnostic Assessments									
Inclusion/Exclusion Criteria	X								
Psychiatric Evaluation & Medical History	X								
Physiological Procedures									
Virtual Examination of Exposure Sites		X	X	X	X	X	X	X	
Urine pregnancy test	X*	X*		X*		X*	X*		
Clinician-Rated Assessments									
Pregnancy Potential/Monitoring Form	X	X		X		X	X		
MGH-SECS-C	X							X	
ADHD-SC		X				X		X	X
CGIs	X	X	X	X	X	X	X	X	X
CTAE	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X
GAF	X	X	X	X	X	X	X	X	X
Progress Note		X	X	X	X	X	X	X	X
Parent-Rated Assessments									
Demographic Interview	X								
SRS-2	X					X		X	X
MGH-SECS-I (Observer)	X							X	
CBCL	X					X		X	
BRIEF-P	X					X		X	
Self-Reported Assessments									
TSRQ			X	X	X	X	X	X	X

*If deemed necessary by the clinician-rated pregnancy potential/monitoring form

3.2 Table II. Flexible Titration Schedule

Day	Maximum Total Dose (minutes)
1 (baseline)	10
7 (week 1)	20
14 (week 2)	30
21 (week 3)	40

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