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Study Protocol:
Evaluation of LED Therapeutic Effect in Youth and Adults with Autism Spectrum Disorder: An Open-Label Pilot Study of a Novel Approach

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List of Abbreviations

ABCL = Adult Behavior Checklist
CBCL = Child Behavior Checklist
ALA = 5-aminolevulinic acid
ASD = Autism Spectrum Disorder
ASRS-SR = Adult ADHD Self-Report Scale
ATP = adenosine triphosphate
AVM = Arteriovenous Malformation
BRIEF-A = Behavior Rating Inventory of Executive Function-Adult Self-Report Version
BRIEF-P = Behavior Rating Inventory of Executive Function-Parent Report Version
CTAE = Clinician-Rated Treatment Emergent Adverse Events Log
CGI-I = Clinical Global Impressions - Improvement
CGI-S = Clinical Global Impressions – Severity
DNA = deoxyribonucleic acid
FDA = Food and Drug Administration
GAF = Global Assessment of Functioning Scale
MDD = Major Depressive Disorder
MGH = Massachusetts General Hospital
MGH-ASD-SCL = MGH Autism Spectrum Disorder DSM-5 Diagnostic Symptom Checklist
MGH-SECS-C = MGH Social-Emotional Competence Scale
OSHA = Occupational Safety and Health Administration
PI = Principal Investigator at the site
Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire
SRS-2 = Social Responsiveness Scale-Second Edition
SSRI = selective serotonin reuptake inhibitor
tPBM = Transcranial Photobiomodulation
TSRQ = tPBM Self-Report Questionnaire

1. 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].

While there is no established pharmacological treatment for the core features of ASD, there are well-established evidence-based pharmacotherapies available for the management of psychiatric disorders in typically developing individuals that frequently co-occur with ASD.

In general, the psychopharmacologic treatment response in ASD populations is atypically associated with higher susceptibility to adverse effects. Treatment literature suggests that compared to general population, individuals with ASD may be more susceptible to adverse responses to medications [4, 5] [6], and this susceptibility could be dose-related [7].

As individuals with ASD are more susceptible to adverse effects, require lower dose initiation and smaller dose titration, and are often unable to swallow pills due to sensory dysregulation, an approach that requires no medication administration may offer better compliance and tolerability. Given that no empirical evidence on this medication in the referenced population is available, a systematic trial on the efficacy and tolerability of extended-release liquid-formulation MPH for the treatment of ADHD in intellectually capable individuals with ASD is warranted.

Because of the limitations of medication treatment in the approach to ASD related social and cognitive deficits, new treatment approaches are required. We propose a novel treatment approach for social and cognitive deficits based on the use of the Transcranial Photobiomodulation (tPBM). The treatment consists in exposing bilaterally the frontal brain to the tPBM, which may enhance ATP production in affected subjects.

The tPBM is a non-ionizing electromagnetic wave. The tPBM is invisible, penetrates the skin and skull into brain tissue, is non-invasive [8], is minimally dissipated as thermal energy and is mainly absorbed by specific chromophores [9]. The benefits of tPBM are wavelength specific. A mitochondrial enzyme, the Cytochrome c oxidase, is the primary chromophore for the tPBM with wavelength around 850 nm [10]. The energy absorbed by the cytochrome c oxidase leads to 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 [10].

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 [11]. These results were confirmed in a different cohort of stroke patients with mild to moderate severity of illness [12]. 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 [11, 12]. The tPBM has also been used as a treatment of alopecia [13] and

in animal models for methanol-induced retinal toxicity [10]. 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. 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 [14]. LED light does not share the same risk level as laser light sources and in our study will have multiple protections to safeguard against this risk.

Proposed treatment with tPBM has been previously studied in patients with Major Depressive Disorder (MDD) [15, 16]. 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 [17]. 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 [18]. 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 [19]. A preliminary open study in 10 depressed subjects has shown that the tPBM was safe, effective and well tolerated [20].

This proposed pilot study will test the efficacy and tolerability of tPBM in patients with Autism Spectrum Disorders. Improvement in executive functions, or anxiety and depression symptoms may contribute to improvement in problems with social cognition among patients with ASD, thus requiring monitoring [21]. Because the tPBM is a non-ionizing radiation, multiple sessions, likely required for the treatment of ASD, are expected to be safe.

The advantage of the tPBM treatment approach as compared to pharmacotherapy is that adherence can be easily monitored and the patient is not required to ingest any substance. It is possible that the exposure to tPBM might be more acceptable than use of medications among some minorities. As compared to talk-therapy, the tPBM therapy has the advantage of not requiring providers with specific cultural expertise or second language proficiency. Our study, although preliminary in nature, will contribute to answer the question of whether tPBM has an effect on ASD symptoms and whether it is acceptable in minority populations, thus justifying further studies and investments.

Our interim analyses from this ongoing study of tPBM in treatment of core symptoms of ASD in adults showed statistically and clinically significant improvements in primary outcome measures of Social Responsiveness Scale-2 (SRS-2) and Clinical Global Improvement Scale (CGI-I). No treatment limiting side effects were noted, and treatment adherence rate was 98%. We now propose to amend existing protocol to include children and adolescents aged 9-17 years (inclusive) diagnosed with ASD, to receive this non-invasive intervention with a benign nature. Analyses of our data reveals this intervention to be safe, tolerated well and acceptable. Age of 9 is determined as the cut off, since CDC reports reveal this age to be the time where social deficits associated with ASD start to manifest, owing to increased normative social experiences of developmentally appropriate school and peer participation demands.

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.

Overview of Niraxx System

There will be 10 Niraxx G1 Headbands 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]. 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.

Titration of tPBM will occur at different rates depending on the age of the subject at the time of treatment. For subjects ages 9-17, energy is administered with a radiation wavelength of 850 nm. The duration of irradiation for subjects ages 9-17 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). For subjects ages 18-59, energy is administered with a radiation wavelength of 850 nm. The duration of irradiation for subjects ages 18-59 is 20-50 minutes at each application site (all sites are irradiated at the same time which is equivalent to 20-50 minutes of total time) (Lampl, Zivin et al. 2007, Schiffer, Johnston et al. 2009, Zivin, Albers et al. 2009). For the detailed titration schedules, please refer to Table II and Table III.

2. SPECIFIC AIMS

The purpose of this 8-week open-label study is to assess the tolerability, safety, and efficacy of Transcranial Photobiomodulation in patients with Autism Spectrum Disorder. Based on our central hypothesis that Transcranial Photobiomodulation will be safe, tolerable, and effective in improving Autism Spectrum Disorder symptoms, we propose to enroll up to 30 subjects of both genders ages 9-59 years (inclusive) with intact intellectual functions satisfying DSM-5 criteria for ASD.

Primary Objective:

- To assess the *efficacy* of the Transcranial Photobiomodulation in patients with Autism Spectrum Disorder across the lifespan

Secondary Objectives:

- To assess the *safety and tolerability* of the Transcranial Photobiomodulation in patients with Autism Spectrum Disorder across the lifespan
- To study the treatment effect of Transcranial Photobiomodulation on mood, social cognition, executive function, ADHD, depression and anxiety symptoms in adults with Autism Spectrum Disorder

3. LENGTH OF STUDY

This study will last up to 12 weeks from enrollment (allowing up to four weeks from the date of consent to schedule and complete the initial screening process). Once subjects have completed the screening process and baseline characterization, they will begin the 8-week open-label trial. Subjects will be assessed on measures of efficacy and safety every week throughout the study.

4. SOURCE OF SUBJECTS

We plan to enroll up to 30 children and adults between the ages of 9-59 in order to achieve the goal of exposing up to 20 subjects. We plan to recruit participants from the referral pool of existing and new patients attending a specialty clinic for ASD at the Massachusetts General Hospital.

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. Adults with ASD, the majority of whom are individuals with intact intellectual capacity and language skills, make up approximately one-third of the ASD population attending the clinic.

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 coordinator to the patient. The patient can then contact the study coordinator for more information on the trial. 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. 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.

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.

5. SUBJECT ENROLLMENT

Informed consent/assent will be obtained remotely prior to administering study related procedures. If a subject expresses interest in the study, the 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 to complete the consent. The study

clinician will have a conversation by phone 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's treating clinician will make all decisions regarding each subject's capacity to provide consent/assent. This decision will be documented via a note to file in the research record.

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.

6. SUBJECT SELECTION CRITERIA

A. Inclusion Criteria

Subjects may be included in the study only if they meet all of the following criteria:

- Male or female participants between 9 and 59 years of age (inclusive)
- Fulfills DSM-5 diagnostic criteria for autism spectrum disorder as established by the clinical diagnostic interview.
- Participants with at least moderately severity of ASD symptoms as demonstrated by SRS raw score ≥ 85 and CGI-ASD severity score ≥ 4
- Participants must understand the nature of the study. If the participant is under the age of 18, the participant's parent/guardian must sign an IRB-approved informed consent form before initiation of any study procedures. Participants ages 18-59 must sign an IRB-approved informed consent form before the initiation of any study procedures.
- Participants must have a level of understanding sufficient to communicate with the investigator and study coordinator, and to cooperate with all tests and examinations required by the protocol.
- Participant experiencing a major psychiatric disorder will be allowed to participate in the study provided they do not meet any exclusionary criteria.
- Women of child-bearing potential must use a double-barrier method for birth control (e.g. condoms with spermicide) if sexually active.
- The subject is willing to participate in this study.

B. Exclusion Criteria

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

- Impaired intellectual capacity (clinically determined)
- Participant is unable to communicate due to delay in, or total lack of, spoken language development (grossly impaired language skills)
- Clinically unstable psychiatric conditions or judged to be at serious safety risk to self (suicidal risk) or others (within past 30 days).
- Subjects currently (within past 30 days) experiencing significant symptoms of major psychiatric disorders as clinically determined.
- Subjects with an unstable medical condition (that requires clinical attention).
- Active suicidal or homicidal ideation, as determined by clinical screening.
- 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 (in US: 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)
- Current treatment with a psychotropic medication on a dose that has not been stable for at least 4 weeks prior to initiating study treatment.
- Investigator and his/her immediate family, defined as the investigator's spouse, parent, child, grandparent, or grandchild.

7. DESIGN

Primary outcome measure will be reduction in ASD symptoms as measured by change from baseline on the self- and/or observer-rated Social Responsiveness Scale-Second Edition (SRS-2) and by the clinician-rated CGI-ASD-Improvement score at endpoint. Responders will be defined as those who demonstrate a ≥30% reduction in SRS-2 total score and/or CGI-ASD-Improvement score ≤2.

Secondary outcome measures will assess for:

1. Treatment-related changes in associated psychopathology, social cognition, executive functions will be assessed by:
    - MGH Social-Emotional Competence Scale (MGH-SEC Scale; clinician- & observer-rated)
    - Social Responsiveness Scale-Second Edition (SRS-2; self- & observer-rated)
    - Adult Behavior Checklist (ABCL; self- & observer-rated) or CBCL where applicable
    - Behavior Rating Inventory of Executive Function-Adult Self Report Version (BRIEF-A) or parent version (BRIEF-P) for youth
    - Adult ADHD Self-Report Scale (ASRS) & clinician-rated Adult ADHD Investigator Symptom Report Scale (AISRS) and CGI-ADHD scale
    - Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q)
    - Hamilton Anxiety scale (HAM-A) & clinician-rated CGI-Anxiety scale
    - Hamilton Depression scale (HAM-D) & clinician-rated CGI-Depression scale
2. Safety and tolerability will be assessed by:
    - The monitoring of spontaneous treatment-emergent adverse events with the Clinician-rated Treatment-emergent Adverse Events Log (CTAE)
    - tPBM Self-Report Questionnaire (TSRQ)

Dosing
The subject will receive daily tPBM treatments for 8 weeks.

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]. 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. 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.

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. Titration of tPBM may occur between scheduled study visits.

Titration of tPBM will occur at different rates depending on the age of the subject at the time of treatment. Titration of tPBM may occur between scheduled study visits. For the detailed titration schedules, please refer to Table II and Table III.

The duration of irradiation for subjects ages 9-17 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).
The duration of irradiation for subjects ages 9-17 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 for subjects ages 9-17 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).

The duration of irradiation for subjects ages 18-59 is started at 20 min per day for the first week (days 1-7), increased to 30 min per day during the second week of treatment (days 7-14), to 40 min per day at week 3 (days 14-21) of treatment. The dose will be escalated to 50 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 50 min daily if no improvement in the context of good tolerability (Table III). Therefore, the duration of irradiation for subjects ages 18-59 is 20-50 minutes at each application site (all sites are irradiated at the same time which is equivalent to 20-50 minutes of total time) (Lampl, Zivin et al. 2007, Schiffer, Johnston et al. 2009, Zivin, Albers et al. 2009).

Subjects diagnosed with ASD who meet all inclusion criteria, have none of the exclusion criteria, and are willing to undergo the Informed Consent process will be eligible to participate in this clinical study.

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.

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.
- 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.
- The participant's weight and height will be measured.
- We will ask the participant or parent/guardian of youth to complete a questionnaire about ASD symptoms (SRS-2). This questionnaire takes approximately 5-10 minutes to complete.
- We will ask the participant or parent/guardian of youth 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 a 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.

Washout Period
After the screening period, subjects who are currently taking prohibited medications 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. If

appropriate, medication washout will be recommended by our clinicians to participants and current providers. Clinicians 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.

Study baseline to Endpoint (week 8)

Participants will be prescribed to administer 2 treatments per week for 8 weeks.
Virtual study visits will have a visit window of +/-3 days to facilitate scheduling. All visits will be conducted virtually via the MGH Telemedicine platform, TeleHealth, which is maintained by Partners HealthCare. In the event that TeleHealth malfunctions or a subject loses access to a device compatible with TeleHealth at scheduled time, the study visit will be completed via telephone call instead.

During the visits, the participants will be asked questions about the symptoms of ASD 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.

At the baseline visit, the subject will be examined via a video call 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 on 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 instruct the subject on the administration of the tPBM with careful observation that the subject appropriately places the headband device. For subjects ages 9-17, 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. Subjects ages 18-59 will be instructed to administer the treatment sessions daily for eight weeks, with each session lasting 20-50 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.

The following assessments will be performed at the Baseline Visit:

- CGIs

- GAF
- CTAE
- Concomitant Medications
- ADHD-SC
- BRIEF-A/P

During study visits:

- A study doctor will ask the participant questions about the participant's ASD symptoms and general health. The study doctor will also ask if the participant is having any side effects, and if they have taken any other medications during the previous week (see Table I for details).
- We will ask the participant to fill out five questionnaires at baseline (beginning of Week 1) and midpoint (end of Week 4) and this will take approximately 30 minutes. We will ask participant to fill out one questionnaire on beginning of weeks 3, and 6 (approximately 5-10 minutes). We will ask participant to fill out six questionnaires at endpoint (approximately 40 minutes). For children under the age of 18, we will ask their parent/guardian to complete these forms.
- Optional: If a parent/caregiver is available, we will ask them to complete three observer- & self-rated measures on the REDCAP at baseline and endpoint. The observer-rated MGH Social Emotional Competence Scale (MGH-SECS-I) will also be administered at midpoint. Aside from the observer-rated MGH-SECS-I, any measures that were completed during the screening visit (week 99) will only be completed again at endpoint.

For quality control purposes, assessments completed during these visits may be recorded. These recordings will be used to monitor quality control and inter-rater reliability in this study. Each recording will be coded with subject initials and an identification number to maintain confidentiality. These recordings will be stored in a password-protected database or on an encrypted external hard drive stored in a locked filing cabinet in a secure office.

Study Discontinuation

We will encourage subjects to continue enrollment in the study via follow-up visits regardless of discontinuation of the tPBM. At the end of the study, we will refer the subjects to their counselor and/or psychiatrist at MGH, 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. If a subject is deemed actively suicidal and is believed to be in imminent danger, the study staff will follow a crisis management plan: keep the subject on the phone and alert a clinician. When the clinician comes to the phone they will assess the situation and determine the appropriate next steps. 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.

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 at any time if any of the following conditions are met:

- Worsening of ASD 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
- Clinical judgment of the investigator

Those subjects who terminate study participation before the completion of the study will be asked to complete all tasks scheduled to take place on the final study visit at the time of study discontinuation.

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.

8. ASSESSMENTS (See Table I for an assessment schedule)

Subjects will be evaluated at biweekly intervals. At each weekly visit, measures of safety and efficacy will be obtained using assessments of psychiatric symptoms and functioning (CGIs, GAF) and measures of adverse effects (CTAE). Additionally, height and weight will be collected during the screening evaluation (week 99) and the final study visit (week 8 or endpoint).-At the midpoint (end of week 4) and final study visits (Week 8 or Endpoint), additional clinician- and subject-rated assessments will be repeated (see below for details). Optional observer-rated assessments will be completed at the baseline (week 1) and final study visits.

All data will be collected and entered into REDCap. 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 RedCap link via encrypted email. The link will not allow the participant to access any other data stored on the password-protected database. Only those subjects who receive the link via 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 study data will be collected in paper form.

Clinician-Rated Diagnostic Assessments
(Administered at screening evaluation)

- MGH Autism Spectrum Disorder DSM-5 Diagnostic Symptom Checklist (MGH-ASD-SCL): The range and severity of subjects' ASD symptoms will be assessed with the clinician-administered MGH-ASD-SCL. This screening instrument adopted items from DSM-5 diagnostic criteria for ASD and assesses for the individual core domains and associated features of ASD.

Clinician-Rated Behavioral Measures
(Administered biweekly)

- Clinical Global Impression Scale (CGI; [22]): 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*, *ASD*, *anxiety* and *depression*.
- Global Assessment of Functioning Scale (GAF; [23]): composite rating of an individual's overall level of functioning (1= worst to 100 = best).

(Administered at baseline, 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.
- Hamilton Anxiety Scale (HAM-A; [24]): a rating scale used to assess anxiety. This questionnaire consists of 14 questions assessing these symptoms. Clinicians are asked to rate each symptom as absent, mild, moderate, severe, or very severe.
- Hamilton Depression Scale (HAM-D; [25]): a rating scale used to assess depression. This is a multiple-item questionnaire used to rate the severity of depression in adults. Clinicians are asked to rate each symptom as absent, mild/trivial, moderate or severe.
- Adult ADHD Investigator Symptom Report Scale (AISRS; [26]): The AISRS, shown to be sensitive to drug effects in adult populations, assesses each of the 18 individual criteria symptoms of ADHD in DSM-IV on a severity grid (0=not present; 3=severe; overall minimum score=0; maximum score=54).

Subject-Rated Behavioral Measures (or Parent/Guardian rated if the subject is <18 years of age)
(Administered at screening evaluation)

- Demographic Interview: This brief interview will collect information regarding socioeconomic status and history of head injury or trauma [27].

(Administered at baseline, midpoint, and final study visits)

- Social Responsiveness Scale-Second Edition Self-Report (SRS-2; [28]): a 65-item rating scale completed by subjects that is used to measure the severity of autism spectrum symptoms as they occur in natural settings.
- Adult ADHD Self-Report Scale (ASRS; [29]): The 18-item ADHD Rating Scale will be completed to evaluate frequency of ADHD symptoms on a scale of 0 to 4.
- Behavior Rating Inventory of Executive Function-Adult Self-Report Version (BRIEF-A; [30]): a 78-item rating scale to assess level of executive function deficits.
- Behavior Rating Inventory of Executive Function-Parent Report Version (BRIEF-P): a 78-item rating scale to assess level of executive function deficits.
- Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q; [31]): a 16-item questionnaire to evaluate the degree of enjoyment and satisfaction experienced in eight areas of daily functioning.

Observer-Rated Behavioral Measures (or Parent/Guardian rated if the subject is <18 years of age)

(Administered at baseline and endpoint)

- Social Responsiveness Scale-Second Edition Informant-Report (SRS-2; [28]): a 65-item rating scale completed by parents/caregivers that is used to measure the severity of autism spectrum symptoms of the subjects as they occur in natural settings.
- Adult Behavior Checklist (ABCL; [32]): An observer-rated assessment of maladaptive behavioral and emotional problems, social competence and substance use in adults ages 18-59.
- Child Behavior Checklist (CBCL): A parent-rated assessment of maladaptive behavioral and emotional problems, social competence, and substance use in children.

(Administered at baseline, midpoint, and endpoint)

- MGH Social-Emotional Competence Scale [Informant-Rated Measure] (MGH-SECS-I): This is a 37-item scale that assesses change in the frequency and severity of core and associated symptoms of ASD.

Clinician-Rated Safety Measures

(Administered at baseline, all treatment visits and at final visit)

- Clinician-Rated Treatment Emergent Adverse Events Log (CTAE): to record any spontaneous adverse health events experienced during the study, along with duration, severity, cause, treatment, and outcome.
- Concomitant Medications: to record additional medications taken during the study.

Subject-Rated Safety Measures

(Administered at weeks 3 and 6)

- 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 week 3 and week 6 of the study (after at least two tPBM sessions have been delivered).

9. DATA ANALYSIS

Statistical Analysis

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). Thus, statistics for paired samples will be utilized. This design largely protects against the bias introduced by confounding factors. That is, since the same participants are tested on two occasions, all static confounding factors are perfectly balanced, and can have no impact on the findings. Bias can still result from time-varying factors that are not associated with the outcomes, but we are confident that any such factors will have a minimal impact on this study considering the duration of the trial. Specifically, we will employ Wilcoxon signed rank tests for continuous or discrete outcome measures, and McNemar's test for binary outcomes. These tests are free from assumptions regarding the distribution of the outcome variables, which is appropriate since the scales we are proposing to utilize are not considered to have Gaussian distributions, and will not be amenable to parametric methods.

10. SAFETY

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, reported adverse events, laboratory tests, and vital signs. 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.

Study Treatment

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.

11. CONFIDENTIALITY

All research-related records initiated as a result of a subject's participation in this study that reveal the subject's identity will remain confidential except as may be required by law. Subjects will only be contacted regarding future studies if they indicate that they are interested in being contacted by initialing in the specific section of the consent form.

12. RISKS AND DISCOMFORTS

Frequent Adverse Events Related to Study Treatment

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.

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 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. Our tight schedule of 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.

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.

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).

13. POTENTIAL BENEFITS

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

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 physical exams 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.

Table I. Study Schema

Weeks	99	0	1	2	3	4	6	8
tPBM Device Subject Training	X	X						
tPBM Treatment (9-17)- 10 min/day		X						
tPBM Treatment (9-17)- 20 min/day			X					
tPBM Treatment (9-17)- 30 min/day				X				
tPBM Treatment (9-17)- 40 min/day					X	X	X	X
tPBM Treatment (18-59)- 20 min/day		X						
tPBM Treatment (18-59)- 30 min/day			X					
tPBM Treatment (18-59)- 40 min/day				X				
tPBM Treatment (18-59)- 50 min/day					X	X	X	X
Diagnostic Assessments								
MGH-ASD-SCL	X							
Psychiatric Evaluation & Medical History	X							
Physiological Procedures								
Physical Examination	X							X
Urine pregnancy test (females only)	X							X
Vital Signs (Height & weight)	X							X
Clinician-Rated Assessments								
MGH-SECS-C		X				X		X
CGIs	X	X		X		X	X	X
GAF	X	X		X		X	X	X
HAM-A	X					X		X
HAM-D	X					X		X
AISRS	X					X		X
CTAE		X		X		X	X	X
Concomitant Medications	X	X		X		X	X	X
Progress Note	X	X		X		X	X	X
Patient-Rated Assessments								
Demographic Interview	X							
ASRS (18+)		X				X		X
SRS-2 (Self/Informant)	X	X				X		X
BRIEF-A/P		X				X		X

Q-LES-Q		X				X		X
TSRQ				X			X	
MGH-SECS-I (Observer)	X	X				X		X
ABCL/CBCL	X	X						X

Table II. Flexible Titration Schedule (Ages 9-17)

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

Table III. Flexible Titration Schedule (Ages 18-59)

Day	Maximum Total Dose (minutes)
1 (baseline)	20
7 (week 1)	30
14 (week 2)	40
21 (week 3)	50

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