Research
Office for Research & Discovery

F200: Application for Human Research

PROJECT TITLE: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of the Safety and Efficacy of Nexalin Electrical Brain Stimulation as an Adjunctive Therapy for Substance Dependence

INVESTIGATOR INFORMATION

Principal Investigator Name,Degree(s):	Michael A. Grandner, Ph.D., MTR, CBSM, FAASM
Affiliation	☒ UA ☐ B–UMG
Principal Investigator **UA NetID**	grandner
Status/Rank:	Assistant Professor
Center:	
Department:	Psychiatry
College:	Medicine
Contact phone:	(520) 626-4746
Official Institutional Email:	grandner@psychiatry.arizona.edu

ADVISORCONTACT INFORMATION (REQUIRED FOR ALL STUDENTS AND RESIDENTS)

Name, Degree(s), **UA NetID**:	N/A
Contact phone:	
Official University Email:	

ALTERNATE/COORDINATOR or CO-PI CONTACT INFORMATION
***THIS INDIVIDUAL WILL RECEIVE COPIES OF ALL CORRESPONDENCE ON THE STUDY**

Name, **UA NetID**:	Pamela Alfonso Miller MD, **palfonsomiller**
Contact phone:	(520) 626-1737
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SECTION 1:REQUIRED SIGNATURES

1. PRINCIPAL INVESTIGATOR

I will conduct my study according to the University of Arizona HSPP policies and procedures for research with human subjects.

		Michael A. Grandner, Ph.D.
Signature	Date	Print Name

2. ADVISOR (FOR ALL STUDENTS AND RESIDENTS ACTING AS THE PI)

I will oversee the student researcher according to the University of Arizona HSPP policies and procedures for research with human subjects.

Signature	Date	Print Name

3.SCIENTIFIC/SCHOLARLY REVIEW(SEEHSPP GUIDANCE ON REQUIREMENTS FOR SCIENTIFIC/SCHOLARLY ASSESSMENT - INCLUDE DOCUMENTATION FOR OPTIONS A AND B WITH SUBMISSION MATERIALS.)

a. ☐ Nationally based, federal funding organization (NIH, NSF) subject to full peer review

b. ☐ Nationally based, non-federal funding organization (March of Dimes, Amer Academy of Pediatrics) subject to peer review

c. ☒ Locally constituted peer review (signature required)

		Richard Lane, M.D., Ph.D.
Signature	Date	Print Name

4. DEPARTMENT/CENTER/SECTION REVIEW

I have reviewed this application and determined that all departmental requirements are met and that the investigator has adequate resources to conduct the Human Research.

		Ole Thienhaus, M.D. / ojt@psychiatry.arizona.edu
Signature	Date	Print Name/Email

5. RESPONSIBLE CLINICIAN (PROJECTS INVOLVING MEDICAL PROCEDURES WHICH THE PI IS NOT AUTHORIZED TO CONDUCT)

I am a clinician licensed by the State of New Jersey. I will be responsible for ensuring that all procedures that are part of this project and that require the attendance of a licensed physician will have a suitable physician present during the procedures. If at any time this is not possible, I will inform the IRB before any procedures are conducted.

		Randa Mind, M.D.
Signature	Date	Print Name

SECTION 2: GENERAL INFORMATION

1. How many Human Research studies does the PI have open? 5

2. How many research staff will be involved in the Human Research? 18

3. What is the expected length of this project? 2 years

4. Will the University of Arizona be the coordinating center for a multi-site study?
☐ No ☒ Yes- Complete Appendix C- Multi-Site study

5. Retention of study materials before, during, and after completion of the project:
a. Where will original signed consent and PHI Authorization documents be stored (building name and room)?Location: UAHS 7th floor, rooms 7326 and 7329

b. How long will consents be maintained after conclusion of the project?
☐ 6 years (UA standard) ☐ 6 years after child reaches 18 ☒ Other (explain): Indefinitely as data may be used for future research

6. Is or will the project be funded by an external funding source e? ☐ No ☒Yes- Complete below:

a. Funding PI: **Michael A. Grandner**
b. Proposal Title: **A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of the Safety and Efficacy of Nexalin Electrical Brain Stimulation as an Adjunctive Therapy for Substance Dependence**
c. Funder Name: **Nexalin, Inc.**
d. Total funding amount **OR** per subject amount: $111,094
e. UAccess Account Information Provide one of the following below:
   i. Institutional Proposal #: 00773108
   ii. Award #:

Submit complete copy, cover-to-cover, of grant or award. If you need help locating any of the UAccess numbers please call Sponsored Projects at 626-6000.

7. Is the project funded by a **For-profit** industry sponsor? ☐ No ☒ Yes- Complete required below:

a. IRB Payment eDoc #: 6557421

*Please review **HSPP Guidance, Fees for Human Research**, for more information.*

8. Conflict of Interest (COI):
The Principal Investigator hereby affirms that ALL individuals who meet the definition of *investigator* for this project in the current *Policy on Investigator Conflict of Interest in Research*

have completed the mandatory Conflict of Interest training and Disclosure of Significant Financial Interests.

☒ Yes ☐ No (explain):

9. Additional requirements:

Certain types of research require additional regulatory documentation. Please identify which of the following apply to your project. Complete the appropriate Appendix and submit as part of the submission materials.

☐Appendix A – Children (subjects under 18)
☒Appendix B – Drugs/Devices (A clinical investigation of a drug or device)
☒Appendix C –Multi-Site study (The UA IRB will review research activities for an investigator or research staff not affiliated with the UA who is 'engaged in the research' (e.g. consenting, collecting data, or analyzing identifiable information)
☐Appendix D – Pregnant Women/Neonates
☐Appendix E – Prisoners
☐Appendix F – Waivers of consent, waiver of a signature, or waiver or alteration of PHI
☐Appendix G – Exception From Informed Consent (EFIC)
☐Appendix H – Native American or International Indigenous populations
☐ None apply to the proposed study

10. Research Site:

Location (Explain): Research will be conducted at the University of Arizona and the Carrier Clinic. All data collection will take place at Carrier Clinic. Data will be analyzed at the University of Arizona Department of Psychiatry.

If research is taking place at B–UMG or AZCC please check the appropriate boxes below:

Banner– University Medicine Group:

☐Phoenix Campus	☐ Biological specimens	☐ Clinical Data
☐ Tucson Campus	☐ Biological specimens	☐ Clinical Data
☐ South Campus	☐ Biological specimens	☐ Clinical Data

**Submit a copy of the UAHS Research feasibility review approval*

University of Arizona Cancer Center:

☐North Campus	☐ Biological specimens	☐ Clinical Data
☐ Orange Grove Clinics	☐ Biological specimens	☐ Clinical Data
☐ Phoenix	☐ Biological specimens	☐ Clinical Data

**Submit a copy of the Scientific Review Committee letter*

SECTION 3. PROJECT NARRATIVE

1) Background

Nexalin brain stimulation may augment existing substance use treatment in a subset of patients. If only a portion of patients are able to benefit with reduced or delayed relapse rates, this would represent an important public health benefit, since substance use treatments are very expensive and are often unsuccessful, leading to associated safety, psychiatric, and medical implications. Also, Nexalin may prove to be a viable option for patients that have failed other courses of therapy.

The Nexalin device produces a waveform that provides transcranial electrical stimulation (TES) to the brain delivered at a frequency of 77.5 Hz. There is evidence that this waveform, at this frequency, results in improved psychiatric outcomes in terms of improved mood, anxiety, and pain. The specific mechanisms of action are not completely understood, but available evidence suggests that this waveform alters the function of the hypothalamus and related structures. In particular, Nexalin may lead to increases in levels of enkephalins and beta-endorphins in brain and CSF. Other data suggest that Nexalin can alter endogenous levels of both serotonin and substance P. It is hypothesized that repeated Nexalin treatments over several weeks can serve to adequately stimulate long-term neurochemical changes.

Nexalin may be a viable adjunctive treatment to substance use disorders. Nexalin is currently being used as adjunctive treatment to substance use disorders in a number of institutions including Behavioral Health of the Palm Beaches in Florida and Carrier Clinic in New Jersey. Anecdotal results are that the treatment is safe and effective. Some of this positive experience in part served as impetus for this formal study.

It should also be noted that the Nexalin device has undergone extensive safety analysis indicating that the device is safe for its intended purpose, and has been in use treating the subject population at the Blake Recovery Center for more than one year. Additionally, the classification of the device places it into a nonsignificant risk (low risk device) category. A review of Phase III Pivotal Clinical Trials (with a follow up period of one year) demonstrates that Nexalin Therapy does not result in any significant adverse events or side effects. In fact, there was no significant difference between reported events in the placebo group and reported events in the active treatment group.

Since the direct electrical stimulation impacts neurotransmitter systems implicated in substance use treatment, and since Nexalin has demonstrated effectiveness in psychiatric conditions while maintaining a favorable safety profile, it is possible that Nexalin treatment could be a viable adjunctive treatment of substance use treatments.

References:

1) L. N. Airapetov, et al. Change In The Beta-Endorphin Levels In Brain And Cerebrospinal Fluid In Transcranial Electroanalgesia. Pavlov Institute of Physiology of the USSR Academy of Sciences, Pediatric Medical Institute, Leningrad, USSR, Physiology Journal (Fiziol. Zhurn). 1985. V. 71. #1. Pg 56-62.
2) Excerpts from a Phase II Study Using Nexalin® Therapy for the Treatment of Depressive Symptoms Associated with Mild to Moderate Depression Episodes; Sponsored by Kalaco Scientific, Inc., Statistical report.
3) Paresh D. Patel, Crystal Pontrello, and Sharon Burke. Robust and tissue-specific expression of TPH2 versus TPH1 in rat raphe and pineal gland. *Biological Psychiatry, Volume 55, Issue 4, 15 February 2004, Pages 428-433*
4) Brain Basics: Know Your Brain. National Institute of Neurological Disorders and Stroke, NIH Publication No.01-3440a, last updated May 01, 2007

5) Neuroscience Tutorial, created by Diana Weedman Molavi, PhD at the Washington University School of Medicine; Washington University Program in Neuroscience, copyright 1997
6) R. Bowen., *Pathophysiology of the Endocrine System – Functional Anatomy of the Hypothalamus and Pituitary Gland* Hypertexts for Biomedical Sciences. Colorado State University. Last updated September 04, 2001.

2) Purpose

Nexalin treatment could be a viable adjunctive treatment of substance use treatments.

PRIMARY OUTCOMES

1. Reduction in depressive symptoms as a result of Nexalin vs Sham
2. Reduction in anxiety symptoms as a result of Nexalin vs Sham
3. Reduction in insomnia symptoms as a result of Nexalin vs Sham

SECONDARY OUTCOMES

1. Reduction of physical discomfort as a result of Nexalin vs Sham
2. Reduction of cravings as a result of Nexalin vs Sham

3) Lay Summary (approximately 400 words)

Nexalin is currently FDA 510-K cleared for the treatment of anxiety depression and insomnia. Previous clinical research was done ex-US. The primary objectives are to confirm the labeling with a study completed in the United States. The secondary objective are to show that Nexalin may be effective in the treatment of patients wishing to return to sobriety. Nexalin does have this labeling ex-US.

Nexalin is a form of transcranial direct current stimulation (tCDS) that has been cleared by the FDA as a safe, non-invasive treatment for anxiety, depression, and insomnia. Nexalin is effective as a supplementary treatment, or can even be used as a substitute for pharmaceuticals. Nexalin is administered by transmitting a gentle waveform through electrode pads placed on the forehead and behind each ear. The exact mechanism by which Nexalin works is unknown, but it is thought that it acts on areas of the brain responsible for mood control. Nexalin has been very successful in not only the treatment of anxiety, depression, and insomnia but also in a wide range of other brain disorders. Following this logic, Nexalin may be an effective supplementary treatment in addiction recovery. The previous clinical research and labeling for Nexalin were completed outside of the United States. Therefore, the primary objective is to confirm the labeling with a study completed in the United States. The secondary objective is to show that Nexalin may be effective in the treatment of patients wishing to return to sobriety.

4) Setting of the Human Research

Data analysis will be conducted at the **University Of Arizona Department Of Psychiatry**. Data will be collected electronically at **Carrier Clinic** using REDCap electronic data capture tools hosted at the Arizona Institute for Clinical and Translational Sciences**.** Data analysis will take place within the UA Psychiatry Department on the 7th floor in suite 7326 and room 7329.

Carrier Clinic is a private, not-for-profit behavioral healthcare system, which specializes in psychiatric and addiction treatment. Carrier treats over 10,000 clients per year. Carrier's system includes an inpatient psychiatric hospital, detoxification and rehabilitation center, an adolescent residential facility, and a fully accredited middle and high school for students classified emotionally disturbed.

5) Resources available to conduct the Human Research

Department of Psychiatry

The Department of Psychiatry Outpatient Clinic occupies approximately 6,000 square feet and consists of 32 exam rooms, with access to CaTS Research Center facilities (described below). The clinic sees approximately 10,000 psychiatry patients per year. Patients are frequently referred by community physicians who are aware of the Department's ongoing commitment to research on mood disorders.

The Department of Psychiatry has an active research program with staff devoted to research administration, including an upper level director and three research specialists (not including project-specific coordinators). All have experience with IRB/regulatory matters and grants administration. Business office staff is knowledgeable in grants finance and accounting, and work-study students devoted to research are available for data entry and other administrative support.

Computer

The home department of the PI, the Department of Psychiatry, provides personal computer resources for word processing, email transmission, internet access, and statistical analysis software for all staff, as well as laser printers, fax machines, scanners and photocopy machines. The University of Arizona maintains full computer and data analytic processing components available to all university faculty on a fiber-optic network system, with automatic daily backup available on a secure server. All computers have networked access to multiple HP printers (desk jet, laser, and color) and one HP 5P color scanner. Software includes Microsoft Office, SPSS statistics software, and Endnote and RefWorks. There is full time computer support in the UA College of Medicine for these resources.

Office Space

The Department of Psychiatry provides Dr. Grandner with office space in the Arizona Health Sciences Center. Additional office and administrative space is available for the project coordinator and study staff in the Department of Psychiatry Research suites.

Carrier clinic:

Carrier Clinic, a behavioral healthcare system, has been a trusted source of compassionate help and supportive healing for patients and their families since 1910. One of the largest independent, not-for-profit behavioral healthcare facilities in New Jersey, Carrier Clinic specializes in psychiatric and substance abuse addiction treatment, and provides a complete array of expert care and education for adolescents, adults, and older adults on the inpatient and residential levels. Outpatient services are provided for ECT treatment and drug abuse addiction. Carrier treats approximately 1,100 clients per year for substance abuse issues alone.

Carrier Clinic is accredited by the Joint Commission, and is a member of the New Jersey Hospital Association (NJHA), the New Jersey Association of Mental Health Agencies (NJMHA), the American Hospital Association (AHA), the National Association of Psychiatric Health Systems (NAPHS), the Somerset County Business Partnership and the Princeton Chamber of Commerce. The Outpatient

Addiction Treatment Services of Carrier Clinic offers comprehensive drug abuse and alcohol addiction treatment to patients and their families when the severity of addictive disease does not require residential treatment. The treatment approach is based on the 12-Step philosophy in tandem with an individualized evaluation and treatment plan for his or her specific needs – one that focuses on understanding the disease concept of addiction, and the need for relapse prevention skills.

All personnel assisting with the study will be CITI certified

6) Study Population

Patients diagnosed with a substance use disorder, including alcohol use disorder, tobacco use disorder, polysubstance use disorder, or other substance use disorder.

INCLUSION CRITERIA

To be included in the study, patients must:

1. Be able to provide informed consent, assessed by the study clinician
2. Be able to speak, read and write fluently in English, assessed by the study clinician
3. Be committed to completion of the study. The subject will need to attest to availability for 10 to 15 treatments over a 5 to 8 day period for the treatment protocol.
4. Be adults over age 18 and under age 65
5. Be actively receiving inpatient substance use treatment for a substance use disorder

EXCLUSION CRITERIA

1. Patients on court-ordered treatment
2. Pregnant or at risk of becoming pregnant
2. Individual has a condition the Investigator believes would interfere with his or her ability to provide informed consent, comply with the study protocol, might confound the interpretation of the study results, or put the person at undue risk

EXPECTED TOTAL SUBJECTS ENROLLED

150

VULNERABLE POPULATIONS

No vulnerable populations will be recruited.

7) Recruitment Methods and Consenting Process

Recruitment Process: Patients will be directly recruited in person from the Carrier Clinic patient population by the clinic's research personnel listed on the F107b, who will already be involved in their medical care. It is expected that the target recruitment of 150 will be accomplished quickly. All patients receiving substance use treatment and otherwise eligible for the study will be approached and asked whether they wish to participate in the research study. All subjects will be in the early stages of returning to sobriety following a period of 72 hour detox. As substance abuse treatment in New Jersey is voluntary, all clients have the cognitive capacity to provide informed consent. Currently substance abuse treatment in the state of New Jersey is voluntary. As participation in this study is voluntary, and the study is taking place on a unit that is voluntary, all clients will initially be considered to be potential study participants. All Blake Recovery Unit clients will be evaluated by the unit doctor to ensure that they met study criteria. Treating physicians will be provided the general study eligibility criteria, and all potential study

participants will be evaluated by their doctor at Carrier Clinic to determine that they meet the criteria whether they might be eligible for study participation. If determined by their doctor to have the ability to provide informed consent, the doctor will then notify the study coordinator. All potential study participants will be evaluated by their doctor at Carrier Clinic to determine that they meet the criteria for study participation.

Upon notification by doctor, study coordinator will approach potential study participants individually and provide a brief description of the study. Those that express interest will have the study explained to them, as well as the procedure associated with participation in the study. The approved informed consent form will be used as the recruitment document and will guide the informed consent discussion. Potential participants will be briefed on how the device works and what participation in the study will entail. All potential participants will be allowed to view the device and room where the sessions will be conducted. After potential participants have been briefed on the study design, potential participants will be presented with the informed consent form (ICF) for their review and for further questions. Upon signing of ICF, participants will be enrolled in the study. Throughout the entire recruitment process potential participants will be informed numerous times that eliciting choosing to participate/not participate will not alter the treatment they receive as patients of Carrier Clinic. At that point, patients will decide whether or not they are willing to continue existing treatment while undergoing Nexalin treatment as well.

Informed Consent: Informed consent procedures will be carried out prior to the subjects' participation in the research study. Subjects will be recruited as detailed above. Potential subjects interested in participating will be able to read the consent form in private. This will afford the prospective subject the opportunity to read the consent form without undue coercion. Thus the individual will have a period in which to determine whether or not they wish to continue. During the subject's initial visit, they will meet with a study clinician, who will describe the study in detail, ascertain eligibility, address any concerns, and obtain written informed consent. The consent form will guide the informed consent discussion. They will be informed that information related to this research study that identifies them and their PHI will be collected from their past, present, and future hospital and/or other health care provider medical records, health records may include information related to the diagnosis or treatment of sexually transmitted disease (STD), acquired immunodeficiency syndrome (AIDS), human immunodeficiency virus (HIV), other communicable diseases, genetic information (e.g., genetic testing), and/or alcohol and/or drug abuse. They will be informed that study staff and study sponsor's monitor may see this information while reviewing their regular health records for this study. Study staff will also stress that declining to participate in the trial will in no way interfere with the subject's relationship to the University of Arizona or Carrier Clinic. They will also be informed that their participation is voluntary and that they can withdraw at any point, again without jeopardizing their standard of care. The study clinicians will take every precaution to ensure that the prospective subject understands what is being asked of them prior to signing the consent form. They will also ensure that they are aware of the risks and benefits associated with the trial. A signed copy will be given to the subject upon completion.

8) Research procedures involved in the Human Research

The baseline assessment will last about 45 minutes and will include measures, taken at the first treatment visit during their inpatient stay:

1. Medical and psychiatric history: Licensed clinicians will interview all patients to document any relevant medical or psychiatric history.

2. SDSCL: The sleep disorders symptoms checklist. The SDS-CL-25 assesses for thirteen sleep disorders and four functional outcomes of sleep. The thirteen sleep disorders include insomnia (initial, middle, and late), advanced sleep phase syndrome (ASPS), delayed sleep phase syndrome (DSPS), OSA, RLS/PLMD, narcolepsy, nightmare disorder, night terror disorder, REM sleep behavior disorder, sleep-related TMJ, sleep insufficiency disorder, shiftwork sleep disorder, EDS not otherwise specified. The four functional outcomes of sleep include night-to-night variability of sleep, daytime dysfunction, and fatigue.
3. RSCAQ: The Retrospective Sleep Continuity Assessment Questionnaire, captures typical sleep habits (time in bed, sleep latency, wake time, wake after sleep onset, final awakenings, amount of naps etc.) and separates them into weekday behaviors and weekend behaviors.
4. PHQ-9: The Patient Health Questionnaire 9 is a brief, well-validated screening tool for depression. Although it only assesses a few symptoms of depression, it has shown good reliability and validity for likely depression diagnosis.
5. GAD7: The Generalized Anxiety Disorder 7 questionnaire is a brief global screening measure of anxiety. It is well validated and is a standard screening tool for anxiety. This scale will allow for separate characterization of anxiety symptoms in addition to depression.
6. CAGE: The CAGE questionnaire is a standard alcoholism screening tool.
7. ASSIST: The Alcohol, Smoking, and Substance Involvement Screening Tool is a validated, standardized instrument used to assess degree of risk for alcohol and other substance use disorders.
8. ISI: The Insomnia Severity Index is a brief insomnia screening tool that is the gold standard for quantifying severity of clinical insomnia symptoms. the ISI is included to account for changes in sleep due to treatment.
9. SAFTEE: The Systematic Assessment of Treatment-Emergent Effects was developed by the NIH to comprehensively catalog any physical symptoms experienced during psychiatric clinical trials along 16 subscales. This measure will be used to systematically measure symptoms and symptom categories.
10. Demographics and Personally Identifying Information: All subjects will report age, sex, education level, race/ethnicity, address, phone number, email, date of birth, medical records number, health insurance information and other relevant demographic and socioeconomic information.
11. Modified Brief Substance Craving Scale.
12. Nicotine use questions: Addresses how much, if any nicotine products (cigarettes, cigars, vapes, chewing tobacco, Nicorette gum, nicotine patches, etc.) were used in a 24 hour timespan
13.
14. Physical Measures: Height, Weight, Blood Pressure: To evaluate basic health measures, all subjects will undergo a basic assessment of height, weight, and blood pressure, using standard clinic equipment.
15. Expectancy: Subjects will be asked to rate on a 100mm visual analog scale, the degree to which they agree with the following statements: (1) This treatment will work, (2) This treatment will help my depression, (3) This treatment will help my anxiety, (4) This treatment will help my sleep, (5) This treatment will improve my quality of life.

Following this baseline assessment, patients will be randomized to receive either Nexalin or Sham treatment. Randomization will occur, such that for every 20 subjects enrolled, 10 will receive Nexalin

and 10 will receive Sham treatment. Sponsor will provide two different devices, identical in appearance and pre-labelled with a sticker (fairy or puppy). One will produce an electrical current, whereas the other will not. Each participant will be assigned a randomization code (fairy or puppy) according to the order of a randomization list generated. Random number generation will be accomplished using the Excel RAND() function.

Nexalin treatment involves placing three conductive pads on the head (one on the forehead and one behind each ear). The patient then sits as the device administers the current through the pads. The default current level for the Nexalin ADI Device is 15.00 mA. This is not adjustable. The treatment is painless. In most cases, patients cannot feel when the pads are activated at all. The pads are activated for 40 minutes during each administration. The Sham treatment will be identical using the same setup procedure, with the exception that there will be no current through the electrodes. Since the Nexalin treatment is undetectable, this will exactly mimic active treatment. Neither subjects nor the study staff will be informed whether they receive active Nexalin or sham treatment, though this information will be made available if medically necessary.

Please see the Nexalin device manual for specific device setup instructions.

All visits will occur on an inpatient basis.

1. Patients will be taken to a standard clinic room, where they would normally meet with their mental health care provider.
2. The health care provider will ask the about their experiences during the week and address any problems with the study.
3. A licensed provider trained on using Nexalin will administer the treatment in two 40 minute sessions. Sessions will occur AM and PM.
4. Subjects will then be free to leave until their next appointment.

During each subsequent treatment visit, subjects will complete the following questionnaires:

1. SAFTEE Physical symptom inventory (see above)
2. Profile of Mood States: The POMS is a standard self-report instrument that assesses clinical and sub-clinical mood symptoms
3. Modified Brief Substance Craving Scale
4. Nicotine use questions: Addresses how much, if any nicotine products (cigarettes, cigars, vapes, chewing tobacco, Nicorette gum, nicotine patches, etc.) were used in a 24-hour timespan
5. Faces rating scale: The scale shows a series of faces ranging from a happy face at A which represents "Happy" to a sad face at G which represents "Feeling bad/sad." Participants will rate their feelings before and after each TES treatment

Also, every three treatments,in addition to the treatment visit questionnaires subjects will also complete the following questionnaires that were administered at baseline: PHQ-9, GAD-7, and ISI.

The final assessment (*after treatment* 15) will include re-administration of all baseline measures, completed at the final treatment visit, with the exception that Expectancy measures will reflect on the treatment, subjects will be asked to rate on a 100mm visual analog scale, the degree to which they agree with the following statements: (1) This treatment worked, (2) This treatment helped my depression, (3) This treatment helped my anxiety, (4) This treatment helped my sleep, and (5) This treatment improved my quality of life.

Thus, each patient will be in STUDY 1 *for 10 to 16 treatments in a 5 to 8 day period*, 2 sessions per day. Sessions will be conducted in AM and PM.
Subjects will be allowed to miss up to 5 treatment sessions within the 1-month treatment window. Any additional missed appointments that are not made up in the stated time frame will be withdrawn from the study.

ANALYSIS PLAN

The results of administering the various tests in a number of metrics that are taken are 4 points:
Pre Treatment
After 5 Treatments
After 10 Treatments
After 15 Treatments
We will compare sham vs Nexalin by measurement over the 4 periods. Comparisons will be done on an absolute basis, percentage basis, from start to measuring point, and for each interval.

9) Cost to subjects

There are no costs to subjects save for their time.

10) Risks to subjects

Risks associated with scheduling and potentially delaying treatment:
Since subjects will still be receiving usual care during the study period, no subjects will be deprived of care at any time.

Risks associated with Nexalin treatment:
Transcranial electric stimulation devices are classified as a Class III device. These types of devices have been used for many years and occasional adverse effects have been reported, including headache, dizziness, nausea, minor burns, increased agitation, minor skin irritation from specific electrodes, and electrical discharge when electrodes are removed. Specifically, headaches and nausea have been noted when current levels are higher than those used in the present study.

To avoid headaches and nausea, lower currents will be used. Patients shall also be instructed to alert the technician if they experience headache or nausea. If the condition continues, treatment will be discontinued. Burn occurrence can be avoided by using lower current (as is in the case for this study), large area electrodes, and by the device's ability to monitor electrode impedance and stop treatment if electrode contact is poor. The device generates no DC current and thus no significant electrolysis will occur in the electrodes. The AC waveform is passed through a charge blocking capacitor to patient electrodes for further patient protection. Rarely, patients have been noted to experience excitability or heightened nervousness during treatment. The technician administering treatment shall be trained to identify such cases and instructed to discontinue treatment as appropriate. If agitation persists for a patient, the licensed health care practitioner may discontinue treatment. Rashes from specific electrodes may occur in patients sensitive to the chemistry used. The possibility of such rashes or skin irritation has been minimized by maintaining charge balance in the output waveform so significant electrolysis does not occur at the electrode/skin interface, and by using glycerol coated electrodes that result in little or no skin irritation. Additionally, collection of patient sensitivity information prior to

treatment may avoid adverse reactions in patients with a prior history. Before treatment, patients shall be instructed to alert the technician if they experience any pain or discomfort. The technician shall also examine the area of electrode contact before and after treatment and note any adverse reactions. Patients will be instructed not to remove electrodes during treatment. Electrodes and wires to the device shall be placed so it is unlikely that electrodes would be accidentally removed during treatment. Finally, patients will be shown the "current off" button on the device and instructed to use this button if it is necessary to terminate treatment prematurely.

However, it should be noted that the current studies deviate from normal care by introducing a relatively low-risk procedure that may obviate the need for a more high-risk procedure. Additionally Nexalin treatments are already FDA cleared for the treatment of anxiety, depression and insomnia. Some of these conditions typically exist in patients returning to sobriety.

Risks associated with Sham treatment:
Since the sham treatment is identical except for a lack of active electrical current, the only risks include those associated with nervousness around the procedure and skin irritation from electrodes, described above. Same protections apply.

Risks associated with questionnaires, interviews, and physical measurements:
As the subjects in the study are psychiatric patients with relatively significant symptoms, and the assessment measures directly address some of these symptoms, it is possible that answering questions in an interview format or in a questionnaire format can arouse uncomfortable feelings or even some level of distress. Although this is very rare, it is possible. It is hoped that the courtesy, professionalism, and experience of these staff members allays any concerns regarding issues arising from the assessments. If subjects are found to be suicidal, they will be discontinued by study clinician (using disqualification form) and treated for their condition, since it is an inpatient population and in active detox, Carrier has the infrastructure and personnel to deal with these situations as they arise

Reproductive risks:
While there are no data to suggest that the effects of this device cause harm to unborn children or children who are breast-feeding, women who are pregnant or breast-feeding are excluded from the present study solely out of an abundance of caution. If the subject is pregnant, it is important that they inform the investigator because they will not be able participate in the study. If the subject states they are pregnant, they will be discontinued by study clinician (using disqualification form) and treated for their condition, since it is an inpatient population and in active detox, Carrier has the infrastructure and personnel to deal with these situations as they arise.

11) Potential benefits to subjects and/or society

It is possible that the Nexalin treatment will ameliorate clinical symptoms. An indirect benefit includes contribution to advancing science.

12) Provisions to protect the privacy of subjects and the confidentiality of data

a. **Protection of subject privacy:** Potential subjects interested in participating will be able to read the disclosure form in private. This will afford the prospective subject the opportunity to read the disclosure form without undue coercion. Thus the individual will have a period in

which to determine whether or not they wish to continue. They will be informed that declining to participate in the sleep research project will in no way interfere with their relationship to their community, the University of Arizona, or Carrier Clinic. They will also be informed that their participation is voluntary and that they can withdraw at any point, again without jeopardizing their standard of care.

b. **Protection of data confidentiality:** All subjects will be identified by code number. Code numbers will be used in all documents for review, evaluation and analyses. No identifiable information concerning a participant will be released. Publication of all results will maintain participant anonymity. Study files for regulatory issues and completed subjects will be kept in a locked file cabinet behind a locked door at the office of the PI at Arizona. Study files for active subjects will be kept in a separate, locked file cabinet in a locked room at the Carrier Clinic. Only those affiliated with the study will have access to these records. Electronic research data will be maintained indefinitely by the UA Department of Psychiatry on servers maintained by the UA College of Medicine, to which only authorized study personnel will be given access. Access will be controlled using login names and passwords unique to each study member, through the secured UA server. All data will be coded to a master list, which will be kept separately from study data in a locked office in the Department of Psychiatry and/or in a password-protected file on secured University of Arizona servers, and will only be accessible to authorized staff until study completion at which time the master list will be destroyed.

13) Access to Private Information

a. **Access to medical records (HIPAA)**: Medical record numbers and Health insurance information will be accessed along with (Name, age, Address, phone number, email and DOB as previously listed), only authorized study personnel will have access to this information. Patients will be de-identified by utilizing a unique system of numbers. Identifying information will not be part of medical records. Subjects will authorize this by signing the IC form (detailed above).

14) Subject compensation

No financial compensation will be provided to participants for participation in the trial.

15) Monitoring for subject safety

Study/Clinic staff will be present and/or available at all times to oversee pertinent study activities and provide or arrange for any necessary care. Adverse events will be reported to the IRB per IRB policies.

All study staff will be trained to handle all study activities within their purview and work with the regulatory coordinator to assure proper oversight and reporting.

Adverse events will be reported electronically by Carrier Clinic to the UA PI via the Adverse Event Report, located on pages 12-13 of the Data Collection Instruments (*NEXALIN data collectN instruments.pdf*), which will be used to collect required AE information. Clinicians will submit all forms as they take the information and data is available to the UA PI in real time. The form contains a provision for ongoing events and further information if required. If adverse events to Nexalin

treatment occur clinicians will use their discretion to handle the situation and report immediately through the tracking form.

The UA PI will review all AE's, serious and otherwise, for submission to the UA IRB per its submission requirements. Unblinding of the treatment received– active Nexalin or sham– will occur if medically necessary to protect the safety of subjects.

16) Medical care and compensation for injury

If subjects experience an adverse event or injury as a direct result of participation in the study, they are instructed to seek treatment and inform their study doctor. The study doctor can assist them in obtaining appropriate medical treatment. If a subject has Medicare or other government health insurance, Nexalin Technologies, Inc. will pay for reasonable medical expenses associated with the treatment of injuries directly resulting from taking part in this research. If a subject has private insurance, Nexalin Technologies, Inc. will pay for these costs to the extent they are not covered by the subject's private insurance. Subjects' health care payers/insurers may not cover costs of research-related injuries.

The University of Arizona and Carrier Clinic have no funds set aside for the payment of treatment expenses resulting from participation in this study. In addition, there are no plans for the University of Arizona or Carrier Clinic to provide other compensation for study-related injuries.

17) Withdrawal of subjects

If disqualifying information/conditions are discovered during screening or at any point during the study, or if it becomes evident that the participant is unable or unwilling to comply with study procedures, research study staff may withdraw that individual from the study.

Subjects can voluntarily withdraw from the study at any time by speaking with the PI or study team. The study staff will then ensure the subject withdraws from the study safely and will provide any necessary follow-up care.

In order to protect subjects, study resources, and the integrity of study data, the Principal Investigator reserves the right to remove any subject at his discretion from the study. This will be communicated to prospective subjects during the consent process.

18) Sharing of results with subjects

Subjects will be immediately informed of any new information that pertains to their rights or welfare or which may alter their willingness to continue participation. Subjects have the right to see and receive a copy of their health information used or created during this study. Subjects request this information from study staff, but they may only receive such information after the study is completed.

19) Future use and long-term storage of data or specimens

Data will be maintained indefinitely for possible use in future unspecified research. Specifically, the following will be retained, linked only to subject ID numbers:

- All sleep related data

- Demographics and personal information (age, sex, education level, relationship status, employment, status, race/ethnicity)
- Medical History
- Family Medical History

20) Clinical Trials.gov Information

Identify if the study is or will require registration on clinicaltrials.gov and who is responsible for registering (e.g. sponsor, contractor, grantee, or awardee). **See HSPP Guidance, Registration of studies on Clinicaltrials.gov.**

☐ ClinicalTrials.gov "NCT" number for this trial (provide):
☒ Registration pending
☐ Clinical trial does not require registration (explain):

SECTION 4: LIST OF ATTACHMENTS FOR THIS SUBMISSION (REQUIRED) (Items listed here are expected to be attached as separate documents. These documents will appear in the UA HSPP IRB approval letter as 'documents submitted concurrently' with the review.)

Document Name	Version Date
1. F107	**1.** 04Oct2017
2. Appendix B (Nexalin)	**2.** 06Nov2017
3. Data collection instruments	**3.** 27Oct2017
4. Nexalin device manual	**4.** 2014
5. FDA 510k clearance	**5.** 21Jul2013
6. Letter RE: Nexalin ownership	**6.** 14Nov2017
7. Appendix C (Carrier)	**7.** 25Sep2017
8. Institutional Agreement – UA oversight	**8.** 27Sep2017
9. F107b	**9.** 31Jan2018
10. Carrier PI CV	**10.** 16Nov2017
11. Consent form	**11.** 01Feb2018
Device Informational Documents:	
12. How Nexalin Works	**12.** 16Mar2008
13. TES Research Articles	**13.**
14. Nexalin Development	**14.**
Publications:	
15. "Common representation of pain…" by Buhle et al	**15.** 17Apr2012
16. "Pain Reduction Using TES…" by Gabis et al	**16.** 2009
17. "Immediate Influence of TES on Pain…" by Gabis et al	**17.** Feb2003
18. "Change in the Beta Endorphin Levels…" by Airapetov et al	**18.**
19. Contract including budget	**19.** 18Oct2017
20. UA PI CV	**20.** 09Jan2017
21. Responsible Physician CV/biosketch	**21.**
22. Responsible Physician license	**22.**
23. Nexalin/Carrier financial information	**23.** 26Jan2018

See HSPP website for submission requirements.

Items needed for approval:

- Word Versions of Application, Consents, Recruitment and Data Collection
- **F107: Verification of Training Form**
- **Current PI/Co-PI CVs or biosketch**, if not included with copy of grant application
- **Informed Consent/Permission/Assent Form(s)** – including study specific release of information documents, DHHS approved sample consent forms. If consent will not be documented in writing, a script of information to be provided orally to subjects

Other Items as applicable:

- **Appendix A - Children**
- **Appendix B - Drug/Device**
- **Appendix C- Multi Site Research**
- **Appendix D- Pregnant Women and Neonates**
- **Appendix E- Prisoners**
- **Appendix F- Waiver of Consent/ PHI**
- **Appendix G- Exception from Informed Consent (EFIC)**
- **Appendix H- Native American**
- **Biosafety Review letter** (for UA - Institutional Biosafety Committee)
- **Certificate of Confidentiality**
- **Compressed Gases Review letter** (for UA – Research Instrumentation)
- **Contract** – complete or draft copy of contract including budget
- **Data Collection Tools** – surveys, questionnaires, diaries not included in the protocol, data abstraction form for records review
- **Data Monitoring Charter and Plan**
- **Drug/Device information** – Investigator's Brochure, drug product sheet, device manual, user's manual, instructions for use, package insert, IND/IDE documentation, FDA 1572 form, 510k indication, FDA exemption, sponsor determination of device risk, etc.
- **Export Control Review**
- **Grant Application(s)** – cover-to-cover copy of grant, regardless of home institution or funding agency, and a copy of the Notice of Grant Award.
- **Multi-site information** (for sites engaged in research where the UA is the IRB of record)
  - Copy of any approvals granted from that site (including determinations if this site has an IRB of its own)
  - Site-specific F107
  - Copy of the site's human subjects training policy
  - CV and medical license (if applicable) of site PI
- **Other Approval letters** (e.g., school districts, Tribal, other IRB approvals)
- **Participant Materials** – written materials to be provided to or meant to be seen or heard by subjects (e.g. study newsletter, physician to participant letter, wallet cards, incentive items, holiday/birthday cards, certificates, instructional videos/written guides, calendars, certification of achievement, etc.)
- **Payer coverage analysis**
- **PHI Authorization Form(s)**
- **Protocol** – including all amendments/revisions, sub- or extension-studies
- **Radiation Safety Review** letter- needed regardless if the radiation device is approved and used standard of care
- **Recruitment Materials** – telephone scripts, flyers, brochures, websites, email texts, radio/television spots, newspaper advertisements, press releases, etc.
- **Scientific Review Committee** letter (for cancer related projects – AZCC SRC; other units as applicable if the unit has a scientific review committee)
- **Site Authorizations** for research purposes and/or access to administrative records/samples
  - External sites (such as schools, other hospitals or campuses, etc.)
  - UAHS Research Portal feasibility review approval
- **Travel Authorization documentation** (for UA – Office of Global Initiatives)
- **Use of retrospective research samples and/or data** – IRB approval letter, original consent under which samples/data were collected, letter allowing access to samples