Cover page:

Title: Investigation of TEST (Transcranial Electric Stimulation Therapy) for Chronic Pain

NCT05113563

IRB approval date: March 26, 2024.

Lay Summary of Proposed Research

This section is intended to provide a basic overview of the study including a description of its purpose, study procedures, and subject population. The summary should provide a concise overview of the study for non-scientific and scientific members of the IRB. Please avoid medical or technical terminology. In general, the abstract of a grant does not provide a suitable lay summary.

About 30% of American adults experience daily chronic pain, which is defined as pain persisting 3 months or more past the expected time of healing that does not resolve with treatment. In addition to considerable suffering, chronic pain is associated with mental illness (including depression, anxiety) and the risk of substance use disorders. Non-opioid medications are recommended but are often don't provide a full response. As a result, opioids are sometimes prescribed, which has the risk of misuse or addiction. Alternatively, patients may resort to other substances of abuse (such as alcohol or cannabis).

Our goal in this study is to investigate TEST (Transcranial Electric Stimulation Therapy) for chronic pain. TEST is similar to electroconvulsive therapy (ECT) in that an electrical stimulus is delivered to the brain. However, the dose of stimulation used for TEST is lower than ECT, and we expect that a seizure will not be generated with TEST (although general anesthesia is required). A previous publication has shown that TEST is effective for treatment resistant depression, without effects on memory that can accompany ECT.

We propose to investigate the feasibility of TEST in subjects with chronic pain. This will be an open-label study where subjects (n=12) are administered 8-10 sessions of TEST over 4 weeks. Measurements of pain, mood, and memory will be obtained before and after the sessions. Our hypothesis is that TEST will be feasible in this subject population and pain symptoms will improve.

Background, Significance, and Rationale

In this section, provide a brief summary of the status quo of the relevant work field and how the proposed study will advance knowledge. Specifically, identify the gaps in knowledge that your project is intended to fill. If no gaps exist that are obviously and directly related to your project, explain how your proposed research will contribute to the overall understanding of your field. Describe potential impacts of your project within your field of study and in a broader context. Provide a critical evaluation of existing knowledge. The literature review does not have to be exhaustive.

Chronic pain non-cancer pain (CNCP) can be difficult to treat, although it affects up to 30% of adults in the United States. While there are non-opioid alternatives for CNCP, such as antidepressants and anticonvulsants, many patients experience only a partial response. For example, with anti-depressant treatment about one in three patients with neuropathic pain will experience a moderate effect on pain relief (Sarto et al, 2010). Anti-epileptic therapies for chronic pain are associated with a high incidence of side effects (Wiffens et al, 2013). Thus, novel treatment approaches are needed for chronic pain.

Electroconvulsive Therapy (ECT) has been in use for decades. The main indications for ECT are treatment resistant depression and refractory catatonia. For these disorders, the efficacy is close to 50-90%. In the past, ECT was used for chronic pain and studies from the 1950s and 1960s reported that ECT alleviated this condition. However, these studies are limited to case reports and studies lacking an appropriate control group. The largest and most recent case series included 21 patients with primary chronic pain who had been refractory to pain treatment (Bloomstein et al, 1996). The patients were treated with ECT (between 5 and 14 treatments). In nine of the 21 patients, the pain syndrome preceded the onset of depression, in another nine patients the pain onset either coincided with or came after the depression, and in three patients the sequence of pain and depression was indeterminate. Of the 21 patients, 19 reported a significant improvement in pain, while one participant experienced no change and one was removed from the study due to medical complications unrelated to ECT (Bloomstein et al, 1996). To our knowledge, the remainder of the literature on ECT for chronic pain is limited to case reports of < 5 patients and range from 1953 to 2020, with no systematic investigation of ECT for this condition. However, these case reports report that ECT was efficacious in reducing chronic pain.

TEST is a form of brain stimulation that resembles ECT, except that the dose is approximately 1/8th the dose delivered in ECT. A recent study showed that TEST is helpful for treatment resistant unipolar and bipolar depression (Regenold et al, 2015; please note that TEST was referred to as 'NET' in this publication). This proof-of -concept trial enrolled 11 subjects who received open label treatment with TEST. The mean Hamilton Depression Rating Scale (HDRS) scores declined significantly with TEST, from 20.3 to 8.6 ($p = 0.001$). Response and remission rates were 73% and 55%. Cognitive testing was done using the Mini-Mental State Exam and the Autobiographical Memory Inventory-Short Form. The results showed that memory was not affected by TEST. In this publication, TEST was delivered at 1/8th the usual ECT dose for 7 seconds. Please note that a sister study is currently being performed at NIMH (in collaboration with our group here at NYSPI) by William Regenold using these same parameters. This protocol will use the same parameters as those used by Regenold et al (2015), as delineated in the procedures section.

The goal of this study is to investigate TEST for chronic pain. Like ECT, TEST will provide widespread stimulation of the prefrontal cortex, including the medial prefrontal cortex (mPFC) and the anterior cingulate (ACC) (Blumenfeld et al 2003 and Lee et al 2016). Imaging studies show that the emotional and cognitive perception of pain are modulated by these brain regions. Using a meta-analytic, data-driven approach, two studies have shown that the ACC and mPFC regulate pain processing (de la Vega et al 2016 and Lieberman et al 2015). Thus, we will investigate whether the stimulation of these brain regions with TEST has an impact on chronic pain.

This is a preliminary, open label feasibility study in adults with CNCP. Subjects will be recruited from the pain clinics of Columbia University Irving Medical Center. Given that this is a feasibility study, it is open to participants with chronic pain caused by a wide range of disorders. Please note that chronic pain, independent of the original etiology, has been shown to involve the medial prefrontal cortex and cingulate. Thus, in this pilot study, the procedure is open to patients with different primary causes of pain who suffer with chronic pain. Subjects will be admitted to the research unit at NYSPI. They will receive three treatments weekly for a total of 8-9 treatments, using the dosing from the previous study of refractory depression (Regenold et al, 2015). Ratings of pain, mood, and memory will be obtained before and after the TEST sessions, and weekly for 4 weeks after the end of the TEST sessions.

Specific Aims and Hypotheses

Concisely state the objectives of the study and the hypothesis or primary research question(s) being examined. There should be one hypothesis for every major study procedure or intervention. For pilot studies, it is important not to overstate the study's objectives. If there are no study hypotheses, describe broad study goals/aims.

Specific Aim 1: We will determine the feasibility of administering NET to participants with chronic pain. Like ECT, NET will be delivered three days a week for three weeks (for a total of 8 to 9 sessions). We will recruit 6 subjects with a diagnosis of chronic pain, defined as pain lasting more than 6 months, that has not remitted with pharmacotherapy, with no other known treatment (examples include chronic postoperative pain, low back pain, musculoskeletal pain, fibromyalgia, visceral pain and neuropathic pain, including complex regional pain syndrome). Our hypothesis is that NET will prove to be safe and tolerable in this patient population and will show preliminary efficacy, defined a priori as a decrease in pain of at least 30%.

Specific Aim 2: We will determine the preliminary efficacy in 6 patients with chronic pain (using the same criteria as above) who have comorbid major depression. We will use the same inclusion criteria and the same outcome measures as Aim 1, obtained before and after the NET sessions. Our hypothesis is that NET will be safe, tolerable, and will have preliminary efficacy on symptoms of major depression in addition to chronic pain (improvement of at least 30%).

Specific Aim 3: We will develop the most appropriate anesthesia regimen for NET. In the past, NET has been delivered using the same anesthesia regimen as ECT. However, since no seizure is elicited with NET, the patient is likely to require only brief sedation rather than general anesthesia for the procedure (as is standard for ECT). Whereas it is typical during ECT to adjust the administered dose of anesthetic medications in subsequent treatments to minimize the time requiring ventilatory/circulatory support and post-ictal confusion, we will determine optimal dosing strategies for NET. We hypothesize that NET participants will require only minimal sedation without neuromuscular blockade.

Description of Subject Population

In this section, you are to describe each subject population of the study. The demographics of the population should reflect the gender and ethnic distribution of each population being studied. Enter each subject population's sample size, Gender, Racial, and Ethnic breakdown, and finally, describe each subject population.

Participants wit Chronic Pain

Subject Population	Number of completers required to accomplish study aims	Projected number of subjects who will be enrolled to obtain required number of completers	Age range of subject population
Chronic pain patients	12	20	22-60

Gender, Racial, and Ethnic Breakdown:

We expect to enroll 50% women; 50% white, 25% black; 25% Hispanic/Latino

Description of subject population: Participants with refractory chronic pain with at least 3 months duration with a diagnosis of chronic postoperative pain, low back pain, musculoskeletal pain, fibromyalgia, visceral pain or neuropathic pain, including complex regional pain syndrome

Suicide Risk Management Plan

This section will include all information regarding the Suicide Risk Management Plan.

This study involves no delay to treatment, no medication taper, all participants receive active treatment. Participants are asked to not change their medication while admitted to the research unit. They can change medications during the follow-up phase. The The Columbia Suicide Severity Rating Scale (CSSRS) will be used at screening, administered by a study physician. Any participant reporting suicidal ideation or behavior (defined as any answer of 'yes' to questions 1, 2 or 6 on CSSRS) to any member of the research team will be evaluated Drs. Martinez, Wai, or Castillo. If the patient is an active suicide risk, 911 will be called and/or the participant will be escorted to the Emergency Department. If the participants is not an active risk, they will be provided with referrals for outpatient treatment. If the participant has outpatient treatment in place, their clinician will be notified. Dr. Martinez, Wai, or Castillo will follow up with the participant until their clinical care is in place.

The C-SSRS is done at screening. After this, the Beck Depression Inventory (BDI) is acquired during the inpatient stay and during the follow up period. The BDI is a self-report measure. The BDI will be used to assess risk and any of the following criteria will trigger a clinical assessment by a psychiatrist regarding suicide risk: 1) an answer of "yes" to question 9 (thoughts of killing self); 2) a score higher than 16; 3) an increase in BDI score of 10 points or more from the baseline BDI (obtained on scan day) even if the total score remains below 16. Please note that the follow up assessments include a phone call with a study psychiatrist. As mentioned above, the psychiatrists are Drs. Martinez, Wai, or Castillo. Participants will be advised that they can call the lab to speak with a psychiatrist when the link is sent. A research assistant will check the responses on the day that they are sent to check the responses**.**

Recruitment Procedures

This section will include all information regarding your study's recruitment process/procedures.

Describe settings where recruitment will occur. Participants will be recruited using advertisments from Facebook and Craig's list (not limited to NYC)

How and by whom will subjects be approached and/or recruited? N/A

How will the study be advertised/publicized? Faceboo and CraigsList

Attach any ads/recruitment materials requiring review at this time in the Uploads section.

Clinical Trials:

Does this study involve a clinical trial? ☐ No ☒ Yes

Please provide the NCT Registration Number for your Clinical Trial. NCT05113563

YOU MUST REGISTER AT ClinicalTrials.gov IMMEDIATELY UPON RECEIPT OF IRB APPROVAL AND PRIOR TO ENROLLMENT OF THE FIRST SUBJECT. YOU WILL BE PROVIDED WITH A NCT REGISTRATION NUMBER ON REGISTRATION. PLEASE REVISE THIS SECTION OF THE PROTOCOL SUMMARY FORM TO INCLUDE THE NCT NUMBER AND RE-SUBMIT AS AN AMENDMENT TO THE IRB.

Concurrent Research Studies

In this section, please identify if subjects in this study participate in or will be recruited from other studies.

Describe where subjects are recruited from. N/A

Describe the recruitment source for (Must provide IRB Number, PI and Title). N/A

Inclusion/Exclusion Criteria

This section details your study sample(s) and addresses the requirement for risk minimization.
You may choose to divide your sample by population (healthy controls vs. patient population) or by procedure (subjects who will have an MRI vs. those who will not) and then define different sets of criteria for each.

For each sample, create or insert a table to describe detailed criteria for study inclusion and exclusion and the method you will use to ascertain each criterion. The method of ascertainment may describe tests, scales and instruments. When relevant, indicate the level of training of the person who will make the assessment (e.g. clinical interview by a psychiatrist).

Inclusion/Exclusion Criteria need to be numbered and listed in outline form (see Table template below).

See record

Consent Procedures

Explain, in this section, the procedures for obtaining consent from study participants.

If the eligibility screening for this study is conducted under a different IRB protocol, enter the NYSPI IRB# N/A

Waiver of Consent / Authorization

The following sections are to be completed for the appropriate waiver/alteration of consent.

Waiver of Consent for use of Protected Health Information (PHI)

What records do you wish to review? N/A

What information are you seeking access to? N/A

Describe your plan to protect identifiers from improper use and disclosure. N/A

Describe your plan to destroy the identifiers as soon as possible, consistent with the conduct of the research, or provide a health or research justification for retaining the identifiers or explain how retention is required by law. N/A

Explain why the research could not be practicably carried out without the information (for which you are requesting access). N/A

Explain why the research cannot be practicably carried out without the waiver. N/A

Explain how/if subjects will be provided with additional pertinent information after participation. N/A

Justification for Waiver or Alteration of Consent

Waiver of consent is requested for the following. N/A

Explain why your research cannot be practicably carried out without the waiver or alteration. N/A

Describe whether and how subjects will be provided with additional pertinent information after participation. N/A

Waiver of Documentation of Consent

Would the consent form signature be the only link between the subject's identity and the research data? N/A

Is breach of confidentiality the main study risk? N/A

Is consent for this research procedure ordinarily not required outside of the research context? Explain. N/A

Describe the study component(s) for which waiver of documentation is requested. N/A

Waiver of Parental Consent

Explain why parental/guardian consent is not a reasonable requirement to protect the minor participants in this study. N/A

If parental consent is waived, describe a mechanism that will be substituted to provide appropriate protections for the subjects. N/A

Assent Procedures

In this section, please describe the procedures by which subject assent will be assessed and / or recorded.

N/A

Persons Designated to Discuss and Document Consent

Please list all the names of persons designated to obtain consent / assent. All persons must complete CITI training for NYSPI. The PI affirms that each name listed has completed the appropriate training.

Screening consent: Alex Grassetti, Natasha DeSilva, Victor Anosike

Study consent: Diana Martinez, MD; Jonathan Wai, MD; Felipe Castillo, MD

Independent Assessment of Capacity

This section is designated for those studies that have been identified where subjects May Lack capacity to consent.

Describe the Methods/procedures for capacity assessment. N/A

If your study involves subjects who DO LACK capacity to consent, please justify. N/A

Procedures for surrogate consent. N/A

Study Procedures

Provide a clear, concise narrative of study procedures with special attention to the subjects' involvement. Detail the overall study timeline and location of study procedures, list all interventions, assessments and interviews, estimate the duration of each procedure, provide dosing schedules, identify study personnel involved in each procedure, and provide

credentials for relevant personnel. If treatment is provided, specify the minimum credentials for providing that treatment. For complicated study designs, we strongly encourage attaching tables, flow-charts, and study algorithms.

Potential subjects are required to have a diagnosis of CNCP, defined as pain that persists or recurs for more than 3 months or past the time of normal tissue healing). A medical and psychiatric interview (by a study physician), ECG, urine toxicology, and labs (comprehensive metabolic panel, complete blood cell count, urinalysis) will be performed during screening.

The following assessments will be obtained during screening:

a) The Hamilton Depression Rating Scale (HDRS): the 24 item assessment scale regarding symptoms of depression.
b) Beck Depression Inventory (BDI): the 21 item self-report rating scale for depression
c) Beck Anxiety Inventory (BAI): the 21 item self-report rating scale for anxiety
d) The Young Mania Rating Scale: a widely used 11 item rating scales used to assess manic symptoms.
e) The Columbia Suicide Severity Rating Scale (CSSRS): a suicide risk assessment that uses a series of simple, plain-language questions to assess thoughts of suicide.
f) The Brief Pain Inventory (BPI): a self-administered questionnaire (0- 10, developed to quantify measures of pain.
g) McGill Pain Questionnaire a self-reported measure of pain studied with a number of diagnoses, and it assesses both the quality and intensity of pain.
h) The Patient-Reported Outcomes Measurement Information System (PROMIS)-29, which assesses pain interference and quality of life.
i) Mini-Mental Status Exam (MMSE), a 30 point a widely used test of cognitive function that includes tests of orientation, attention, memory, and language. The minimum score allowable for study entry is 24.
j) The Timeline Followback (TLFB): a clinical research tool used to obtain quantitative estimates of alcohol, tobacco, cannabis, and other drug use (including prescribed medications, like opioids and benzodiazepines). We will ask about substance use for the month prior.
k) The Defense and Veterans Pain Rating Scale (DVPRS), a graphic tool that clinicians use to facilitate self-reported pain from patients, including the supplemental questions. The DVPRS is similar to the BPI but is more widely used in Veteran populations.
l) MRI safety screening form: standard form used to assess for metal and other risks associated with MRI.

Following screening, participants who are eligible will be consented for the full study. This will include a review of the procedures and risks of the study. Participants will be informed that all procedures are voluntary and that questions can be asked at any point. The consent form can be signed either though REDCap with an e-signature or in person.

Participants will be asked if they want to provide information for an emergency contact, which is not mandatory, on admission to the inpatient unit.

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The additional assessments obtained on the scan (baseline) day include:

a) Columbia Autobiographical Memory Interview – short form (AMI-SF), which is used to assess memory changes in studies of ECT.
b) Trail Making Test (TMT), Parts A and B, to assess executive function.
c) The Stroop Color Word Test to also assess executive function.
d) Repeatable Battery for the Assessment of Neuropsychological Status, which is a brief, individually administered battery to measure cognitive decline or improvement across five domains: immediate memory, visuospatial skills, language, attention, and delayed memory.
e) Montreal Cognitive Assessment (MoCA), a quick (5-10 min) measure of cognition which uses a 10-item, 30-point (30=best score) scale.
f) The Timeline Followback (TLFB): to obtain quantitative estimates of alcohol, tobacco, cannabis, and other drug use (including prescribed medications, like opioids and benzodiazepines). We will ask about substance use for time between screening and baseline.

TEST sessions: Following the MRI and safety read of the scan, subjects will be scheduled for the TEST sessions. Participants will be asked to have no food or drink after 9 pm the night before (NPO). The following assessments will be obtained during the inpatient admission after TEST sessions start.

a) The Brief Pain Inventory (BPI): a self-administered questionnaire (0- 10, developed to quantify measures of pain (weekly)
b) Clinical Global Impression (CGI) scale, a measure of symptom severity, treatment response and the efficacy of treatments as measured by a study physician (three days week).
c) Beck Depression Inventory (BDI): the 21 item self-report rating scale for depression (weekly).
d) Beck Anxiety Inventory (BAI): the 21 item self-report rating scale for anxiety (weekly).
e) The Defense and Veterans Pain Rating Scale (DVPRS), a graphic tool that clinicians use to facilitate self-reported pain from patients, including the supplemental questions (weekly).

Subjects will be asked to confirm that they have had no food or drink for 8 hours with the exception of required prescription medication which they can take by mouth on the morning of the procedure with a small sip of water. They will then be asked to change into a hospital gown, escorted to the ECT suite. Vital signs (blood pressure, heart rate, and oxygen saturation) will be recorded at baseline and every 5 minutes through the end of the procedure. EEG leads will be placed in the middle of the forehead and on the left mastoid to monitor for any seizure activity. The EEG output will be reviewed to assess the absence of a seizure.

General anesthesia will be performed by an anesthesiologist. TEST will be sub-convulsive, but since seizure threshold determination for ECT involves sub-convulsive stimulation and is done routinely, there are no substantial differences or additional risks with TEST.

The absence of a seizure will be verified per usual ECT protocol by observing for tonic-clonic movements in a lower extremity isolated from neuromuscular blockade by a blood pressure cuff maintained above systolic blood pressure and with interpretation of the electroencephalogram (EEG) generated from the electrodes placed in the center of the forehead and one each on the left and right mastoid processes.

In the event that a subject has a seizure, the TEST dose will be lowered to 1/10th of the ECT dose (from 1/8th). The seizure will be discussed with the participant, including the plan to reduce the dose. If a participant has a seizure at 1/10th dose, they will be discontinued from the study.

Subjects will be monitored until they recover. The subjects' oxygen saturation, BP and heart rate must be back at baseline before discharge (oxygen saturation >95%, BP and HR within normal limits and within +/- 10 mmHg or BPM). The expected recovery time is 60 to 80 minutes. Subjects will remain in the recovery area until they are assessed by the physicians and ready to leave the ECT suite. Subjects will return to the inpatient unit after each TEST session when they are awake from anesthesia and have stable vital signs**.**

At the end of the TEST sessions, subjects will be asked to complete the following assessments prior to discharge from the unit:

a) The Hamilton Depression Rating Scale (HDRS): the 24 item assessment scale regarding symptoms of depression.
b) The Brief Pain Inventory (BPI): a self-administered questionnaire (0- 10, developed to quantify measures of pain
c) The Defense and Veterans Pain Rating Scale (DVPRS), a graphic tool that clinicians use to facilitate self-reported pain from patients, including the supplemental questions.
d) Columbia Autobiographical Memory Interview – short form (AMI-SF), which is used to assess memory changes in studies of ECT.
e) Trail Making Test (TMT), Parts A and B, to assess executive function.
f) The Stroop Color Word Test to also assess executive function.
g) Repeatable Battery for the Assessment of Neuropsychological Status, which is a brief, individually administered battery to measure cognitive decline or improvement across five domains: immediate memory, visuospatial skills, language, attention, and delayed memory.
h) Beck Depression Inventory (BDI): the 21 item self-report rating scale for depression
i) Beck Anxiety Inventory (BAI): the 21 item self-report rating scale for anxiety
j) The Patient-Reported Outcomes Measurement Information System (PROMIS)-29, which assesses pain interference and quality of life.
k) McGill Pain Questionnaire a self-reported measure of pain studied with a number of diagnoses, and it assesses both the quality and intensity of pain.
l) Clinical Global Impression (CGI) scale, a measure of symptom severity, treatment response and the efficacy of treatments as measured by a study physician.
m) Montreal Cognitive Assessment (MoCA) test: a brief, simple screening for cognitive impairment.

Prior to discharge, participants who are not engaged in treatment for their chronic pain will be assisted with finding medical care for this condition. They will also be referred to psychiatric care if depression emerges or persists during the study. Please note: while participants are asked to not change their medication while admitted to the research unit. They can change medications during the follow-up phase.

We will ask subjects to speak with us by phone weekly for a month. They will also be asked to complete the TLFB (with study clinician) at this time (for the past week). Subjects will also be asked to complete the brief pain inventory, the Beck Depression Inventory (BDI); the Beck Anxiety Inventory (BAI); and will be asked about any change in medications (by phone).

Participants are followed by a study physician if they experience an adverse event (whether study related or not) until it resolves. This procedure will occur even if the follow up visits have been completed. Participants are also offered the option of being followed by a study physician until they have a visit with their health care provider.

Participants can opt to have the study PI communicate with their treating physician. This requires the completion of a release of information form. The communication between the PI and their physician would include a discussion of their diagnosis, previous treatment, study procedures, and outcomes.

After discharge from the study, participants are followed for 4 weeks with physician visits (telephone) and assessments (

I attest to follow the COVID-19 Safety Guidelines for Columbia Psychiatry and NYSPI Re-Entry outlined in the NYSPI Director's June 1st memo, which include but are not limited to:

- Infection Control/PPE – Guidelines
- Research participants will only come on-site if absolutely necessary for study procedures.
- No volunteers/externs on-site during Stage 1.
- Clinical research teams will screen their participants for COVID symptoms (night before and day of onsite visit, documenting this in the chart), and escort them in and out of the building.
- COVID/COVID-like symptoms in participants will be reported to the IRB via PRISM as an SAE.

Analysis and Outcomes

This protocol consists of an early feasibility study. Thus, all participants will receive active stimulation (no sham group) using an open-label design enrolling 12 participants. We have chosen this sample size in order to assess the following outcome measures: willingness to participate, tolerability, cognition, and pain. The willingness to participate will be assessed by measuring the percentage of participants who enroll out of those who are screened for the study. We expect that at least 20% will agree to enroll.

Criteria for Early Discontinuation

Define criteria that will be used to exit or drop subjects from the study and operationalize. Indicate the time points when such criteria will be applied, and describe the rating instruments, parameters, and thresholds that will lead to a decision

to terminate a subject's participation and the role of the person who will make these determinations. Studies which include a medication taper and discontinuation may be asked to include an independent medical monitor (an MD not on the study team) who will aid the study team in determining whether study discontinuation is needed. In addition, explain procedures for managing subjects who are withdrawn from the protocol.

For treatment studies: To minimize risks to subjects, operationalized drop-out criteria should be defined so that subjects who worsen, or in some cases, fail to improve, are removed from the study and offered standard care. The threshold for drop-out should consider the level of risk associated with non-improvement for the specific disorder, the availability of alternatives, and the typical required duration of treatment. For example, emergence of suicidal intent, or psychosis, should prompt immediate clinical evaluation and withdrawal from the study.

Participants will be discontinued if they have two seizures. In the event that they have one seizure the TEST dose will be lowered to 1/10th of the standard ECT dose (from 1/8th). The seizure will be discussed with the participant, including the plan to reduce the dose. If a participant decides to continue, this will be documented in their chart. If a participant has a seizure at 1/10th dose, they will be discontinued from the study.

Blood and other Biological Samples

Describe how the sample will be used and indicate, when relevant, the amount of the sample. The IRB wants to know that the sample is sufficient for the purposes of the study, but that sampling is limited to what is minimally necessary.

If you've indicated that you intend to store a sample for future use, indicate where the sample will be stored, how long the sample will be stored, and to what purposes the sample will eventually be put. Check the IRB website at https://irb.nyspi.org/investigators/guidance/genetic-research for specific guidance and additional information about future use of DNA samples.

Blood samples will be obtained for labs during screening (20ml) as will urine (<20 ml) for pregnancy testing. No samples will be stored for future use.

Assessment Instruments

List all assessment instruments, indicate who will administer them and their credentials/qualifications. Provide an estimate the duration of each measure. The IRB wants to know that assessments instruments are appropriate measures for the purposes of the study and are no more burdensome than necessary. The IRB will consider the burden of assessment instruments (in terms of time, sensitivity of material, etc.) in the risk/benefit analysis. Please attach copies or otherwise provide all non-standard instruments.

a) The Hamilton Depression Rating Scale (HDRS) the 24-item assessment scale regarding symptoms of depression.
b) Beck Depression Inventory (BDI): the 21 item self-report rating scale for depression
c) Beck Anxiety Inventory (BAI): the 21 item self-report rating scale for depression
d) The Young Mania Rating Scale: a widely used 11 item rating scales used to assess manic symptoms.

e) The Columbia Suicide Severity Rating Scale (CSSRS): a suicide risk assessment that uses a series of simple, plain-language questions to assess thoughts of suicide.
f) The Brief Pain Inventory (BPI): a short, self-administered questionnaire using a 0 to 10 scale, developed to quantify measures of pain.
g) The Patient-Reported Outcomes Measurement Information System (PROMIS)-29, which assesses pain interference and quality of life.
h) Columbia Autobiographical Memory Interview – short form (AMI-SF), which is used to assess memory changes in studies of ECT.
i) Trail Making Test (TMT), Parts A and B, to assess executive function.
j) The Stroop Color Word Test to also assess executive function.
k) Repeatable Battery for the Assessment of Neuropsychological Status, which is a brief, individually administered battery to measure cognitive decline or improvement across five domains: immediate memory, visuospatial skills, language, attention, and delayed memory.
l) Montreal Cognitive Assessment (MoCA), a quick (5-10 min) measure of cognition which uses a 10-item, 30-point (30=best score) scale.
m) Clinical Global Impression (CGI) scale, a measure of symptom severity, treatment response and the efficacy of treatments as measured by a study physician.
n) The Timeline Followback (TLFB): to obtain quantitative estimates of alcohol, tobacco, cannabis, and other drug use (including prescribed medications, like opioids and benzodiazepines). We will ask about substance use for time between screening and baseline.
o) The Defense and Veterans Pain Rating Scale (DVPRS), a graphic tool that clinicians use to facilitate self-reported pain from patients, including the supplemental questions.

Sections to be completed for studies using IND/IDE Drugs and Devices.

Prior to the submission of any study involving a faculty held IND or IDE being approved by the IRB, the IND/IDE holder is required to submit a form signed by the IND/IDE holder and PI.

Which are applicable to your study: ☐ Drug ☐ Device ☐ Radiolabeled drug/compound

Off Label and Investigational Use of Drugs

Enter the information for all drugs to be used in this study:

Name of the drug	N/A
Manufacturer and other Information	
Approval Status (select one)	IND application is pending IND is approved

	No IND is required
IND #	
Who holds the IND (i.e., IND Sponsor). If other than PI/CU Investigator, type name of holder.	
Which applies:	FDA has determined the IND is not required FDA conditions are met (see "Rules") – Explain

Off Label and Investigational Use of Devices

Enter the information for all devices to be used in this study:

Name of the device	Thymatron
Manufacturer and other Information	Somatics, LLC
Approval Status (select one)	IDE is approved
IDE #	G210112
Who holds the IDE (i.e., IDE Sponsor). If other than PI/CU Investigator, type name of holder.	Diana Martinez
Is the device marketed?	No
Which applies:	FDA conditions are met, IDE approved

Off Label and Investigational Use of Radiolabeled Drugs / Compounds

Enter the information for all radiolabeled drug/compounds to be used in this study:

Name of the radiolabeled drug/compound	N/A
Manufacturer and other Information	

Approval Status (select one)	IND application is pending IND is approved RDRC approval is pending RDRC is approved No FDA/RDRC approval is required - Explain
IND #	
Who holds the IND (i.e., IND Sponsor). If other than PI/CU Investigator, type name of holder.	

Research Related Delay to Treatment

Research involving participants who are in need of treatment invariably involves delay to care, and this delay is associated with risk. Scheduling of procedures must be carefully organized to minimize delay. Other delay must involve only that minimally necessary to accomplish the aims of the research while respecting subject well- being and safety. Describe the delay, by virtue of research participation in this study, before a participant can receive treatment of known efficacy or standard care routinely offered in the community.

There is no delay to treatment.

Clinical Treatment Alternatives

Describe what other treatment or assessment options are available to subjects who do not participate in research.

The alternative is for subjects to not participate and to continue their usual care.

Risks/Discomforts/Inconveniences

"Risk" is a broad term used to convey the potential for harm, burden, and inconvenience related to research participation. Use this section to provide a comprehensive description of foreseeable physical, psychological, social, interpersonal, and economic risks introduced by the research. Include the source of the information. Consider both the probability and magnitude of harm and its impact. Describe the foreseeable harms associated with the research (untoward effects of a medication) and those related to delay to individualized treatment. Include data from the literature, and local data, if available, on risk rates and subject experiences with research procedures. Describe

procedures in place to minimize risk. In general, please create a numbered list of risks/categories of risk, and in general put the list in the order of significance or level of risk, the most significant risks should be listed first.

Risks of TEST: Previous experience with TEST is limited to patients with major depression, as describe by Regenold et al, 2015. In this publication, TEST was delivered at 1/8th (which is the same as 1/16th age) the usual ECT dose for 7 seconds. Please note that a sister study is currently being performed at NIMH (in collaboration with our group here at NYSPI) by William Regenold using these same parameters. This protocol will use the same parameters as those used by Regenold et al (2015), as delineated in the procedures section.

Although not intended, a seizure is possible with the delivery of TEST. We do not expect a seizure to occur, as we are using the lower dose of TEST (reported in Regenold et al, 2015). If a seizure occurs, the subject will be monitored as though they have received ECT. Following this session, they will be informed of the seizure and asked if they would like to be removed from the protocol or continue. If they chose to continue, the dose will be lowered by 25%. If another seizure is elicited, they will be monitored appropriately and then removed from the protocol. Based on the previous publication by Regenold et al (2015) we do not expect a seizure to occur. Nonetheless, participants will be informed of this possibility and the need to stop the study.

The anesthesia medications include glycopyrrolate, methohexital sodium, and succinylcholine. The risks of glycopyrrolate include anti-cholinergic effects (dilated pupils, increased body temperature, fast or irregular heart rate, blurred vision, constipation, drowsiness, dry eyes, dry mouth, flushing, and light sensitivity). The risks of methohexital sodium include drowsiness, nausea, vomiting, stomach pain, chills or shivering, coughing, hiccups, muscle twitching, or mild skin rash or itching. The side effects of succinylcholine include jaw rigidity, hypotension, muscle fasciculation, respiratory depression, and salivary gland enlargement. Rare side effects include a severe allergic reaction, malignant hyperthermia, transient residual weakness due to prolonged succinylcholine activity (due to pseudocholinesterase deficiency, which is exceedingly rare [approximately 1 per 2000 to 5000 people] but would make succinylcholine last longer than 3-5 min), myoglobinuria/myoglobinemia, and arrhythmias.

Other risks of TEST include:

1) An adverse reaction to anesthesia is a rare but potentially severe complication. This is related to the anesthetic agents and neuromuscular blockade. This is mitigated by medical screening, the appropriate monitoring, and clinical management should a reaction arise.
2) Blood pressure changes are common but are usually transient and manageable. Both hypertension and hypotension may occur, and subjects will be monitored for these issues. Cardiovascular complications are not common but possible. These include arrhythmias and/or ischemia. This risk is mitigated by monitoring by the anesthesiologist.
3) Pulmonary complications such as aspiration pneumonia, bronchospasm, transient and even life-threatening decreases in blood oxygen saturation are possible during general anesthesia for any procedure. In this study, this risk is specifically mitigated by excluding patients with known pulmonary disease, active pulmonary infection, recent or persistent COVID-19 infection, evidence of low blood oxygen saturation levels (SpO2 < 95%) at baseline, known history of airway difficulty, and morbid obesity. Given the transient need for ventilatory

support for TEST, the risk of reduced pulmonary capacity of function after TEST is small and would be on par with ECT, perhaps even less than ECT given that the goal of TEST is to avoid seizure activity. These risks will be mitigated by monitoring by the anesthesiologist.

4) Dental and oral trauma is possible, though not common. This includes dental fractures, lacerations, and prosthetic damage. This risk is mitigated by the removal of prostheses and the use of mouth protection during the procedure.
5) Pain and discomfort is seen with ECT, but we expect this to be less likely with TEST. This can be addressed with ibuprofen if needed.
6) A prolonged seizure is not expected, but possible. The anesthesiologist will administer methohexital or propofol, as is standard for ECT in the event of a prolonged seizure. This decision will be made by the ECT anesthesiologist.
7) Skin burns are uncommon and typically mild. They can occur when there is poor contact of the electrode with the skin surface resulting in high impedance in the electrical circuit. Skin burn risk will be mitigated by proper skin preparation and the use of conductivity gel under each stimulus electrode.
8) Additional potential risks include short term memory loss and difficulty learning.

The risks of drawing blood include bruising, bleeding, or (rarely) infection (phlebitis). These risks are avoided by using proper blood drawing technique.

The risks of the questionnaires include boredom, becoming tired, or finding questions uncomfortable. These risks are reduced by asking only what is necessary, letting participants take breaks as needed, and clarifying that these assessments can be stopped if needed.

Methods to Protect Confidentiality

Describe the data management plan and the methods you will employ to protect subject privacy and the confidentiality of research data. The section should detail how information will be collected, recorded, coded, stored, transmitted, and as applicable, shared with other investigators so as to minimize risks related to breach of confidentiality. Confirm that identifiers are removed, to the extent possible, from research data, and explain if there are links between subject identity and research data, or if the data are anonymous. Also, indicate where the data are stored, who is responsible for data safekeeping, and who has access to subject identity and codes, if any, which cross-link research data and subject identity. Confirm that identifiable data are not collected, stored, or transmitted by mail, fax, on removable drives, laptops, or via the internet without proper protections, e.g. encryption.

Participants divulge information, for example, regarding drug use, which is sensitive and may have adverse social consequences if released. We deal with issues of confidentiality by using coded records, storing signed consent forms in a locked safe, and try to the best of our ability to maintain confidentiality. Data are kept on a password protected computer, and if there is any electronic transmission concerning the study, it will use numeric identifiers rather that participant names. Further, we will use HIPAA-compliant platforms to questions about participants and to sign this consent form (Redcap and Qualtrics).

We also point out to prospective participants that we cannot assure that their drug histories and other personal records might not become known. Those who are hospitalized have hospital charts and we cannot guarantee the confidentiality

of these. In addition, we inform volunteers that we must conform with NY State reporting requirements (e.g., child abuse). In addition to a discussion of this topic, the information is clearly stated in our consent forms. Participants in other studies have understood this and have agreed to participate under these conditions.

We are collaborating with the lab of Bashar Badran, PhD, at the Medical University of South Carolina, who will model the electrical field generated by TEST. To accomplish this, MRI scans will be sent to MUSC. The MRI scan files do not contain PHI and the scan itself is not considered PHI (per Rachel Marsh, PhD, director of the MRI core. The consent form makes this clear to participants. It also says that participants are not required to agree to have their MRI shared in order to participate. In this case, a note will be included in their file and the MRI will not be sent.

Some participants completed the study prior to this collaboration. Thus, I will call these three participants to discuss the option of allowing us to share their MRI scans. If they agree, consent will be obtained either through RedCap or by mailing a consent form addendum (along with a return envelope).

Will the study be conducted under a certificate of confidentiality?

☐ Yes, we will apply for the Certificate of Confidentiality

☐ Yes, we have already received a Certificate of Confidentiality

☒ No

Direct Benefits to Subjects

Describe only benefits to individual subjects that are likely to accrue during the study itself. Do not include subject compensation or treatment to be provided at the end of the study, as these do not figure into the IRB's risk/benefit considerations. Do not describe diagnostic and evaluation components unless subjects receive clinical feedback. Do not describe the anticipated scientific benefits of the research. Some studies offer no direct benefit to subjects.

This study is not designed to benefit participants directly

Compensation and/or Reimbursement

If compensation or reimbursement for expenses will be offered to subjects, please describe and indicate total amount and schedule of payment(s). If transportation is reimbursed, state if receipts are necessary for reimbursement. Include justification for compensation amounts and indicate if there are bonus payments.

Data Management Plan

All federally funded, more than minimal risk studies are required to include a Data Management Plan. The required elements of the Data Management Plan include: identification of the database platform (e.g., REDCap) and inclusion of an attestation that it is Part 11 compliant, identification of a qualified staff member who designs and maintains the database, design and implementation of data system training for all Principal Investigators & research coordinators & all protocol staff, and significant changes to the data management plan will be submitted as protocol amendments in PRISM. More information can be found on the IRB website at https://irb.nyspi.org/forms regarding this plan and should be reviewed prior to submission.

The plan was submitted and is approved.

References

Please limit references, preferably no more than twenty.

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