Study Protocol and Statistical Analyses Plan
for ClinicalTrials.Gov

The Safety and Efficacy of Nexalin Trans-cranial Electrical Stimulation for the Treatment of Depression

NCT # 03277846

January 10th 2017

ORIGINAL PROTOCOL

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of the Safety and Efficacy of Nexalin Electrical Brain Stimulation for the Treatment of Depression in Patients Referred to Electro-Convulsive Therapy

SHORT TITLE

Nexalin Treatment Study

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FINANCIAL INTERESTS

No investigators or consultants have a financial interest in Nexalin TES.

PROJECT FUNDING INFORMATION

Project funded by Nexalin, Inc.

STUDY SITES: DESCRIPTION AND RESPONSIBILITIES

The Carrier Clinic is a large, well established, psychiatric care facility that has been in operation since 1910. It 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 organization has not regularly engaged in clinical research and it is for this reason that they, along with Nexalin, sought out a partnership with the University of Penn Behavioral Sleep Medicine Program (Penn BSMP) and the Penn Human Subjects board to provide guidance and oversight with respect to the proposed protocol. The protocol was developed by investigators at Penn (Drs. Grandner & Perlis). All data acquisition, data management, and human subject oversight will be the sole province of the Penn collaborators. Carrier Clinic's role is to recruit subjects and to conduct the Nexalin treatment. Carrier Clinic personnel have extensive training and experience with brain stimulation via ECT and specific training from Nexalin regarding the safe and effective use of Nexalin based transcranial electrical stimulation (TES). Twenty eight members of the Carrier Clinic staff have attended a 75 minute training program. Each training was conducted by personnel from Nexalin (2 individuals) who collectively have 300 hours experience with the device and method (and have been certified by Nexalin re: the device use). Each training included lectures covering:

1) History of TES, how the method is similar and different from other related methods (e.g., TES vs. AV stimulation, Neurofeedback, TMS, and ECT, etc.), and

2) Procedures for use, and safety considerations.

This information was also made available via the provision of a treatment manual and a video. The trainings also entailed 6 hours of supervised hands-on training with the TES device (one treatment series for those that administer the intervention). At present, the CC has conducted TES as a regular intervention for patients in approximately 60 individuals cared for at the Carrier Clinic, since 0ctobet 2015. This translates to about 20 interventions with TES per week. Note: the Nexalin TES device has been cleared for clinical use since 2003 (See 510K FDA approval document and the device manual, Appendix 1) and it is estimated that the device is in regular use at 35 locations in the US and with about 7,500 patients treated to date.

All participating staff and subjects will complete, in addition to the traditional paperwork and charting processes associated with standard clinical care, study documents via a password protected RedCap site on a Penn Server. These documents will be reviewed by the study coordinator on a daily basis and with the Penn PI on weekly basis. As needed reviews with the PI will occur given the incidence of an adverse event, the occurrence of treatment non-response, the incidence of patient non-adherence, or the occurrence of protocol deviations. In addition to the daily review of the study progress and problems, the study coordinator will speak on a bi-weekly basis with the Carrier Clinic coordinator and complete a checklist and notes form to document these encounters. The PI and coordinator will travel to the clinic once a month to discuss study logistics.

The study documents will include the following

a) A subject identification form
b) A study consent form (completed on paper w/ a signed digital copy sent to Penn staff via a secure upload method)
c) 10 study questionnaires (e.g., the PHQ-9) completed by the patient via a RedCap site on a Penn Server according to a pre-determined schedule.
d) 5 Tracking forms (re: patient contact, procedure details, and adverse events) completed by Carrier Clinic staff via a RedCap site on a Penn Server according to a pre-determined schedule

BACKGROUND

Electroconvulsive therapy (ECT), also referred to as "electroshock therapy," is a psychiatric treatment where external electrical stimulation (brief-pulse currents of up to 800 milliamps) is used to induce seizures. Treatments are administered, with anesthesia and muscle relaxants, 1-3 times per week over the course of several weeks, or until symptoms improve. ECT is very effective as an antidepressant, reducing depressive symptoms in approximately 50% of patients. Despite its effectiveness, it comes with significant risks. It can cause mild or severe confusion and memory loss, muscle soreness, worsening of symptoms in patients with neurologic disorders, and (as with any procedure that involves sedation), adverse effects from hypoxia. Finally, patients may also be disinclined to engage in this form of therapy owing to the social stigma associated with it and concerns about side effects. Accordingly, an alternative to ECT would be beneficial.

Nexalin transcranial electrical stimulation TES) may represent an alternative to ECT, for at least a subset of patients. This form of therapy (if found to be efficacious) may be more acceptable to patients given it does not require the elicitation of seizures, the use of sedation, and/or have the side effects (or social stigma) of ECT. Further, the course of treatment may be shorter than ECT, depending on the frequency or duration of TES therapy administration (treatments may be administered up to 100 minutes per day [as specified in the 510k summary document]). Finally, the reduced expense of TES may be important as it may prompt clinicians and third party payers to advocate for this form of treatment where they might not with ECT.

The Nexalin device, FDA clearance (501K=K024377, Classification: Stimulator, Cranial Electrotherapy: CFR 882. 5800: U.S. Patent #6904322B2), produces a square waveform that provides transcranial electrical stimulation to the brain delivered at a frequency of 77.5 Hz at 0 to 4 mA peak current. There is evidence that this waveform, at this frequency, results in improved clinical outcomes in terms of anxiety and pain. The specific mechanisms of action are not known, but available evidence suggests that this waveform alters the function of the hypothalamus and related structures. In specific, TES may lead to increases in levels of enkephalins and beta-endorphins in brain and CSF. Other data suggest that TES can alter endogenous levels of both substance P and serotonin. Regardless of which neuropeptide or neurotransmitter is ultimately found to be modulated by TES, it is hypothesized that repeated TES treatments over time serve to stimulate long-term neurochemical changes.

TES (as administered by the Nexalin apparatus) may be a viable alternative to ECT. A prior randomized, controlled trial compared antidepressant medication with Sham TES, Placebo with Nexalin at a lower dose, and Placebo medication with Nexalin at a higher dose. All three conditions showed remission of depressed mood by the end of treatment and maintenance of remission status following 12 weeks of follow-up. Thus, the effect sizes for Nexalin treatment were comparable to antidepressant medication. It should also be noted that the Nexalin device has undergone extensive safety analysis indicating that the device is safe for its intended use. 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 TES 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.

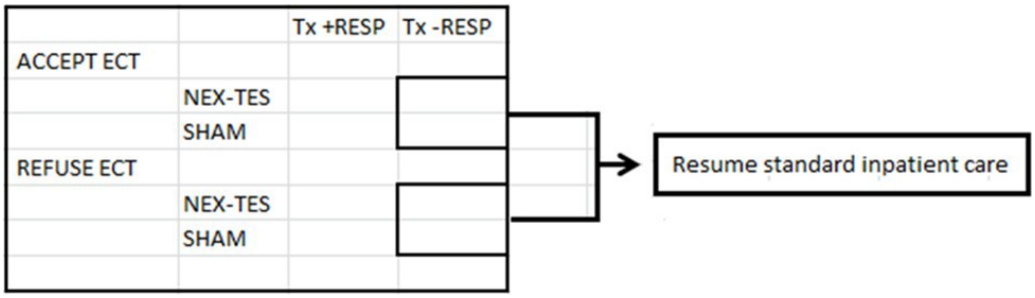
Since the direct electrical stimulation represents a similar mechanism of action to ECT, and Nexalin has not only demonstrated effectiveness in depression but also has a much better safety profile than ECT, it is possible that Nexalin treatment could be a viable, more acceptable, alternative to ECT.

STUDY GOAL

Determine whether Nexalin TES is a viable alternative to ECT in subjects who do and do not accept ECT treatment.

STUDY DESIGN

A 2x2 factor Randomized Controlled Trial with block randomization. Inpatient subjects at the Carrier Clinic who are referred for ECT will be recruited, typed regarding their acceptance of ECT, and randomized to either treatment with TES or to a Sham condition. Treatment non-responders in either condition will continue as in patients at the Carrier Clinic until they reach acceptable levels of functioning to be discharged. For additional details, see "procedures" section of this document.



STUDY DURATION

The study will last up to 2 years. This will allow sufficient time for recruitment and completion of all subjects.

TARGET POPULATION

Patients diagnosed with major depressive disorder (MDD) who have failed antidepressant therapy with one or more medications and are referred for ECT.

INCLUSION CRITERIA

To be included in the study, patients must be:

1. In-patients at the Carrier Clinic
2. Adults over age 18 and under age 65
3. Able to speak, read and write fluently in English, assessed by the study coordinator at Carrier Clinic
4. Screened Negative for alcohol abuse and/or dependence
5. Able to provide informed consent, assessed by the study coordinator at Carrier Clinic
6. Referred for ECT
7. Not currently taking hypnotics or be prescribed hypnotics during the Nexalin trial.
8. Not pregnant or intending to become pregnant during the study
9. Committed to completion of the study.

TOTAL SUBJECTS ENROLLED

150

VULNERABLE POPULATIONS

No vulnerable populations (as defined by socio-economic status, geography, gender, age, disability status, and other populations identified to be at-risk for health disparities) will be recruited.

RECRUITMENT & RADOMIZATION

As noted above, patients will be directly recruited from, and receive treatment at, the Carrier Clinic. Currently, the Carrier Clinic treats approximately 1,000 unique patients who receive ECT annually, resulting in 5,200 procedures performed per year. Randomization will occur in blocks, such that for every 20 subjects enrolled, 10 will receive Nexalin and 10 will receive Sham treatment.

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

PRIMARY OUTCOMES
Percent responders and non-responders to TES treatment or Sham TES treatment (who accepted or refused ECT) as assessed with the PHQ-9 (50% reduction or a score below 10).

SECONDARY OUTCOMES
Assess whether Nexalin TES produces significantly greater gains than Nexalin Sham for

1. Depression severity (as assessed with the PHQ-9, and the QIDS)
2. Anxiety severity (as assessed with the GAD-7 and the POMS)
3. Insomnia severity (as assessed with the ISI)

Finally, we will (post hoc) assess which baseline subject characteristics differentiate between responders and non-responders.

PROCEDURES
All patients referred for ECT and otherwise eligible for the study will be approached by the Carrier Clinic study coordinator (or his designate) and asked whether they wish to participate in the research study. All subjects will be non-responders to traditional medical approaches (patients diagnosed with MDD who have failed antidepressant therapy with one or more medications). Those that express interest will review the study protocol with the study coordinator. The study coordinator will ascertain eligibility, address any concerns, and obtain written informed consent. Following the obtention of informed consent, the subject will be scheduled (or undergo at the time) a baseline assessment. The subjects that volunteer, are eligible, and are consented for the study will be queried as to whether or not they are willing to receive ECT. This decision will be used to type each subject that consents to be in the protocol (Accept or Refuse ECT). Following randomization to one of two conditions (TES or Sham), treatment will occur twice daily (40 minutes per session, separated by 5 hours' time between the AM and PM sessions) over 3-10 days. Subjects that do not exhibit 20% attenuation of symptoms (as assessed by an AM and PM version PHQ-9) on or before 6 treatments will be designated treatment non-responders and discontinue their participation in the study while remaining as inpatients at the Carrier Clinic. Note: During the Nexalin trial, all subjects will receive standard inpatient care where the only difference in the treatment regimens are that they are receiving TES or Sham TES in place of ECT. See "Protection Against Risks" section for stopping rules during treatment for subjects who do not show sufficient treatment response.

Session Protocol. The protocol for receiving treatment will be as follows:

1. Inpatients that have enrolled in the study will receive TES or Sham TES once in the AM and once in the PM.
2. The procedure will be conducted in a semi-private room while the subject reclines in a lounge chair.
3. The two TES session will each be 40 minutes in duration, separated by 5 hours' time.
4. The TES provider will oversee the administration of the patient on-line questionnaires.
5. The TES trained provider will complete the Carrier Clinic staff forms.
6. When the TES session is complete, the subject will resume his/her regular clinic activities.

Treatment. As noted above, Nexalin TES or Sham TES will be administered twice per day (9am noon and then again 2pm-5pm), Monday through Friday, over the course of 3-10 days. Each patient will receive a minimum of 6 treatments and may receive up to 20 treatments depending on whether an adequate treatment response is observed during the first 6 session (this is based on the assessments overseen by the Penn staff based on the AM/PM PHQ-9 evaluations). All procedures will be performed at the Carrier Clinic facility by licensed

personnel with experience providing care to medication non-responders and will be specially trained on using the Nexalin equipment. Nexalin TES 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 waveform generated by the Nexalin device is a high frequency square wave (100 kHz), which has its amplitude modulated at a frequency of 77.5 Hz. Amplitude of the waveform (square wave pulse) is controlled to range from 0 to 4 mA peak current (off is 0 mA and on is 4mA). Each treatment session will last for 40 minutes. The treatment is not expected to be painful, but some individuals may experience discomfort (i.e. tingling and burning). In most cases, patients cannot feel when the pads are activated. The Sham treatment will be identical with the exception that there will be no current through the electrodes. Since the Nexalin treatment is undetectable, this will exactly mimic active treatment.

Assessments. Assessments will be made at baseline (pre-treatment), twice daily, once daily, and once every 3 days (6 sessions). All assessments will be administered on-line via two web-sites dedicated to the study (1 website for the subjects and one website for the clinical staff). The subject web-site will contain 10 questionnaires. The staff website will contain 5 forms.. See figure below for a specification of the specific instruments and schedule of administration. The site itself will be built using Research Electronic Data Capture (REDCap) software. Note: All data acquired via this method (raw and summary data) will not be available to the Carrier Clinic collaborators during the study.

	#	Instrument	Time Required	Baseline	Each Session	Q 3 days	Pre-Post	PRN
Patient	1	Demographics	5 min	●				
	2	AFQ & CAGE	2 min	●				
	3	Patient Expectancy	1 min	●				
	4	QIDS	5 min	●		●		
	5	ISI	2 min	●			●	
	6	SAFETEE	5-10 min	●		●		
	7	PHQ-9	1 min	●	●			
	8	GAD-7	1 min	●		●		
	9	POMS	10 min	●		●		
	10	FACES	1 min		●			
Clinician	1	Patient Enrollment	2-5 min	●				
	2	Procedure Tracking	2-5 min		●			
	3	Adverse Event	5 min					●
	4	Clinician Information	2-5 min	●				
	5	SBJ d/c Form	2-5 min					●

ASSESSMENT OF SUBJECT CLINICAL STATUS

As noted above, patient status will be assessed at baseline, twice daily (pre-post each session), once daily, and once every three days. The instruments will be administered on-site via an internet data portal (constructed with RedCap).

Subject Measures. All self-report instruments used in the study are listed below along with their administration schedule and a brief explanation regarding what the instrument measures.

1. Demographics *(completed once at baseline / intake):* All subjects will report age, sex, education level, **race/ethnicity**, and other relevant demographic and socioeconomic information.

2. AFQ * CAGE (*completed once at baseline / intake*): These instruments are standard alcoholism screening tools. Subjects who screen positive for alcoholism will not be included in the study.

3. Patient Expectancy *(completed at baseline):* Subjects will be asked to rate on a 0-5 Likert 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.

4. QIDS *(completed at baseline and once every three days):* The 16 item Quick Inventory of Depressive Symptomatology (QIDS) is designed to assess the severity of depressive symptoms. The QIDS is a self-administered instrument that assesses all the criterion symptom domains designated by the DSM-IV. The patient is asked to rate the severity and frequency of specific symptoms present over the last 7 days. Each item is interval scaled from 0 to 3. It takes approximately 5 to 7 minutes to complete and the total score is obtained by adding the scores. The summary score ranges from 0 to 27. Threshold values are as follows: ≤ 9 (Not Depressed); 10-13 Mild Depression; Moderate to Severe Depression 14-17; > 18 Severe Depression.

5. ISI *(Completed at baseline and at the end of treatment):* The Insomnia Severity Index is a brief insomnia screening tool that is the gold standard for quantifying severity of clinical insomnia symptoms. This will be administered at the beginning and end of treatment (e.g., 1st and 10th session).

6. SAFTEE *(completed once every 3 days):* 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.

7. PHQ-9 *(completed in the AM and PM session):* The Patient Health Questionnaire 9 is a brief, well-validated screening tool for depression. It has shown good reliability and validity for likely depression diagnosis and provides a means of assessing depression severity. The instrument in the present study has been modified so that it may be 1) administered twice daily and 2) used to track nightly sleep via 4 sleep related items

8. GAD7 *(completed at baseline and once every 3 days):* 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.

9. POMS *(completed at baseline and once every 3 days):* This is a 37-item adjective checklist where each item is rated on a 0-4 unipolar scale that ranges from not-at-all to extremely. The scored instrument provides values for six constructs including: tension-anxiety; depression-dejection; anger-hostility; fatigue-inertia; vigor-activity; and confusion-bewilderment. The outcome variables are measured in terms of the 6 factors and a total score, which are arrayed as T-Scores (standardized means of 50 +/-10).

10. "Faces" Mood Rating Scale *(completed daily pre-post to each TES session):* This is a single item 7 point bipolar rating scale for mood (from very happy to very sad). The measure is arrayed from -3 to +3.

Clinician Measures. All the clinician instruments to be used in the study are listed below along with their administration schedule and brief explanation regarding what the instrument measures

1. 1. Patient Enrollment Form / Candidate Screener / Enrollment Form *(completed once per week per patient):* This requires the staff member to profile the patient who has been approached to participate in the study and to document if they meet eligibility and have been consented.

2. Procedure Tracking form / Patient Tracking (*once per session*)*:* This requires the clinician to record: the patient initials; the patient PNC ID; the date of the session; the session #; the time session was conducted; the room the session was conducted in; the identifying sticker attached to the device; the device number; whether each instrument was administered; any comments they may have about the session; whether the

patient was diagnosed with any new disorders (and if yes, please list); and whether the patient's meds have been changed (and if yes, please list).

3. Adverse Event Form (*completed as needed*): This requires the clinician to record: the patient initials; the patient PNC ID; the date of the session; description of event; information about the event onset; start date and start time of event; information about the event offset; end date and end time of event; actions taken or treatments given; the severity of the event; event symptoms; diagnostic results; information about outcomes; and if the event is on-going what additional steps are planned.

4. Clinician Information Form (*completed once*):
This requires the clinician to record: the study clinician identification number, the clinician's name, the clinician's position at the clinic, the clinician's credentials (degree), and the clinician's contact information.

5. SBJ d/c Form (*completed as needed*):
This requires that a staff member specify that a subject has been withdrawn from, or quit, the protocol and the reason for why the subject is no longer participating.

ANALYSIS PLAN

The primary analysis for the study will be an evaluation of treatment response rates using an analysis of 2x2 contingency tables, using the Cochran-Mantel-Haenszel test to assess differences in treatment response by randomization groups, stratified by patient choice. The secondary analysis will evaluate how treatment non-responders and responders differ with respect to the various demographic and clinical profile measures.

CONFIDENTIALITY

Confidentiality of all paper documents will be maintained by storing all such materials in a locked filing cabinet and only research staff and authorized members of the IRB and OHR will have access. Electronic data will be protected by separating patient identifying information from their assessment data. The former exists on one password protected website (staff website) while the latter exists on a second password protected site (subject website). In both cases, as is standard with RedCap, neither portal allows for administrative access (access to data). The websites only allow for data entry per session. Administrative access (access to both staff and subject data) may only occur via a separate URL which is also password protected. Only Penn staff have administrative access to this URL (i.e., no faculty or staff from Carrier Clinic or Nexalin may access the backend of the patient and staff survey). Access can be granted to the IRB and OHR. The PHI to be collected; who will use the information within the institution and why; who may disclose the information and to whom; the subjects rights to access research information and their right to withdraw authorization (approval) for any future use of personal health information are all listed in the HIPAA form specific to the research The names of subjects and any other identifying information will be kept in a different secure location. The research data will be kept a maximum of three years after study completion. Should publications result from this study, all PHI will be removed.

PERSONALLY IDENTIFYING INFORMATION

The following information will be collected from patients:

- Name
- Age
- Address
- Phone Number
- Email Address
- Date of Birth
- Medical record numbers
- Health insurance information

POTENTIAL STUDY RISKS

Risks associated with scheduling and potentially delaying treatment:

The typical wait time for ECT is 1 week. The proposed study, which lasts up to 10 days may delay access to ECT treatment by between 3-5 days. While such a delay is within the limits of normal wait times, it nevertheless represents a potential delay in accessing a therapy which is known to be effective (ECT).

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, nausea, minor burns, increased agitation, minor rash 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. Note: the device settings for current and duration of treatment are fixed (i.e., cannot be altered by the administering clinician or technician).

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 about the procedure and skin irritation from electrodes, described above.

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.

Risks associated with loss of confidentiality:

There is a possibility that records associated with the study (particularly paper documents such as those in the study binder) will inadvertently be seen by Carrier Clinic personnel that are not affiliated with the study.

Risks associated with ECT

While there are risks associated with ECT treatment, the provision of this therapy occurs outside the proposed protocol and therefore is not a risk of the proposed study.

PROTECTION AGAINST RISKS

Nexalin and Sham: To avoid headaches and nausea, only lower currents will be used (4mA) in association with active treatment. 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 is avoided by using lower current, square wave pulses 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 decrease current or 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 adhesives 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 such that accidental removal of electrodes during treatment is unlikely. Finally, patients will be shown the "current off" button on the device and instructed to use this button if they feel it is necessary to terminate treatment prematurely.

Questionnaires, interviews, and body measurements will be conducted by licensed professionals who are experienced working with mentally ill patients. It is hoped that the courtesy, professionalism, and experience of these staff members allays any concerns regarding issues arising from the assessments.

Study files that exist regulatory issues will be kept in a locked file cabinet behind a locked door at the office of the PI at Penn. 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.

POTENTIAL STUDY BENEFITS

It is possible that the Nexalin treatment (for those randomized to this condition) will ameliorate clinical symptoms.

RISK/BENEFIT ASSESSMENT

Greater than minimal risk. 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. Thus, the potential benefits to the individual, as well as the information gained, outweigh the risks.