Study Initiation Visit

Vielight Depression Study

Protocol No: VL-2023-MDD-PILOT

Study Devices: Vielight Neuro Rx Alpha and Neuro RX Gamma

PI's: Dr. Danilo de Jesus & Dr. Reza Zomorrodi

Co-Investigators: Dr. Genane Loheswaran & Dr. Janine Liburd

SIV Date: 04-JAN-2025

AGENDA

1. Protocol Overview
2. Study Procedures
3. Medical Devices
4. Equipment
5. Study-Specific SOPs
6. Data Collection
7. Investigator and Study Team Roles and Responsibilities
8. Safety and Adverse Events
9. Monitoring and Audits

PROTOCOL OVERVIEW

1. Background
2. Objectives
3. Study Design
4. Risks/Benefits and Risk Mitigation
5. Recruitment and Enrollment
6. Eligibility Criteria
7. Lifestyle Considerations

Background Information

- Major depressive disorder (MDD) is a leading cause of disability worldwide
- MDD has an average lifetime **prevalence of 12%**
- Twice as prevalent in women than men
- **Symptoms:**
  - Persistently low or depressed mood
  - Anhedonia or decreased interest in pleasurable activities
  - Feelings of guilt or worthlessness
  - Lack of energy
  - Poor concentration
  - Appetite changes
  - Psychomotor retardation or agitation
  - Sleep disturbances
  - Suicidal thoughts

Background Information

- **MDD diagnosis:**
  - Requires **five** of the symptoms
    - One must be **depressed mood** or **anhedonia**
      - Causing **social/occupational impairment** during the same 2 week time that represents changes in cognitive functioning

- Abnormalities in **serotonin**, **norepinephrine** and **dopamine** underlie depression
  - Thus, treatments include:
    - Selective serotonin receptor inhibitors
    - Serotonin-norepinephrine receptor inhibitors
    - Dopamine-norepinephrine receptor inhibitors

Background Information

- Preliminary studies suggest that photobiomodulation (PBM) may have potential as a treatment for MDD
  - Askalsky & Iosifescu, 2019; Caldieraro & Cassano, 2019

- The use of pulsed PBM has been demonstrated to modulate brain activity
  - Zomorrodi et al., 2019

- **It is unclear whether pulsed PBM may impact the effectiveness for MDD differentially.**

Study Objectives

Primary Objective: To determine the safety and efficacy of using PBM at personalized alpha vs. gamma frequencies to treat the primary depressive symptoms of MDD.

Secondary Objective: To determine the efficacy of using PBM at personalized alpha vs. gamma frequencies on anxiety symptoms in patients with MDD and to determine the effects of PBM at personalized alpha vs. gamma frequencies on short term memory, sleep, pain and rest/ERP EEG on patients with MDD.

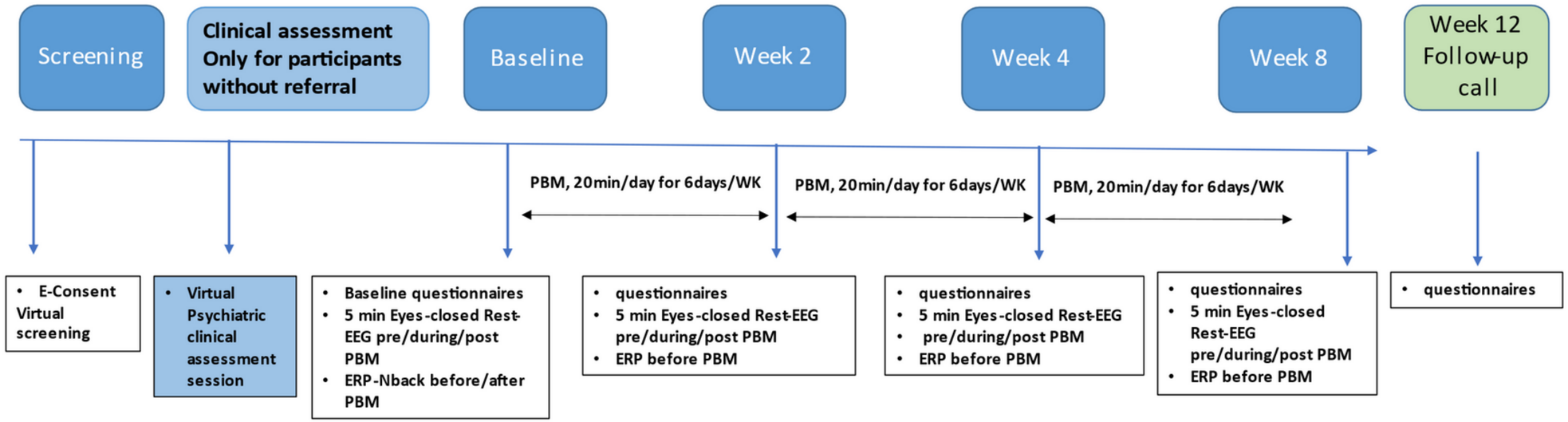
Safety Objective

To determine the safety of using PBM at personalized alpha and at gamma (40Hz) in terms of adverse events and serious adverse events.

Study Design

- **Randomized three-arm, double-blind, prospective, sham-controlled trial**

Three arms study:
1- Personalized Alpha (N=25)
2- Gamma (40 Hz, N=25)
3- Sham (N=25)



Risk & Mitigation

Risk	Description	Mitigation Strategy
Device-related	Nosebleeds, redness, or irritation of the nostril Individuals prone to nosebleeds may have nosebleeds as result of intranasal diode may also be a risk of infection if not cleaned properly between uses	• Provide clear instructions on how to use the device appropriately • Instruct to discontinue use and contact study staff if device-related risks occur • Instruct to seek medical attention if the bleeding is severe
EEG-related	Mild headaches, irritation, slight redness, or itching at electrode sites on scalp	• Monitor and adjust if needed during visits
Privacy-related	Loss of privacy and confidentiality if the PDF copy of ICF is viewed and/or stored on a personal electronic device (especially if the device is shared with others or is lost, hacked, or subject to search warrant or subpoena)	• Inform participants of the risk of saving and viewing the ICF PDF in their personal devices in the ICF
Unknown or unforeseeable risks	Possible unforeseen adverse device effects Unknown whether effects of device are safe during pregnancy	• Inform participants of any new information as soon as possible • Will not include pregnant persons in the study – participants will be informed to notify study staff if they become pregnant

Benefits

No direct benefit to participants

- **Clinical Improvement:**
  - Potential reduction in depressive symptoms (MADRS scores).
- **Innovative Treatment:**
  - Non-invasive, adjunctive PBM
- **Scientific Contribution:**
  - Adds evidence to PBM efficacy for MDD
  - Explores personalized frequency optimization (alpha vs. gamma)

Recruitment

- Potential participant recruitment utilizing a variety of recruitment methods
  - Advertisements
  - Social media
  - Physician referral

- Recruitment rate is based on subject availability

INCLUSION CRITERIA

- 18-60 years age
- Willing to sign the consent form
- **Current diagnosis of MDD, confirmed via doctor's note or clinical assessment**
- Mild to severe depression (MADRS ⩾17)
- Are agreeable to keeping their current antidepressant treatment constant during the intervention
- If on antidepressant treatment, they must be on a stable dose of antidepressant (6weeks)
- Have had no increase or initiation of any psychotropic medication in the 4 weeks prior to screening
- Capable of speaking English to comply with study procedures

EXCLUSION CRITERIA

- Active alcohol and/or substance use disorders in the past 6 months assessed by AUDIT & DAST -10
- Pregnancy
- Current major psychiatric or neurologic disease such as current and/or lifetime psychotic episodes, bipolar disorder psychotic symptoms, history of stroke or seizure
- Treatment -resistant depression (more that 2 FDA approved antidepressant medication trial failed during current depressive episode) or any failed FDA approved device -based intervention.
- Implant in the skull and/or brain
- Active suicidal ideation, or/ and homicidal ideation
- Anticonvulsant medication use benzodiazepine use (equal or greater to lorazepam 2mg)
- rTMS or ECT treatment within 4 weeks prior to study
- Ketamine use
- Current unstable medical condition or significant disease that may affect efficacy or safety assessments, or any other reason which, in the investigator's opinion, may preclude the subject's participation for the full duration of the trial
- Skin photosensitivity
- History of Lyme Disease

Lifestyle Considerations

Daily Device Usage

- 20 min/day, 6 days/week, for 8 weeks
- Log each session in daily diary

Medication Stability

- Maintain stable antidepressant dose (≥6 weeks)
- No psychotropic medication changes during the study

Restricted Treatment

- Avoid rTMS, ECT, and ketamine during the trial

Health Monitoring

- Report adverse effects promptly
- Attend scheduled follow-up visits
- Record device usage after each session in daily diary

STUDY PROCEDURES

1. E-Consent and Screening
2. Baseline Visit
3. Follow-up Visits (Week 2,4,8)
4. Week 12 Phone Call
5. Subject Withdrawal

E-Consent

- Potential study subjects will be sent digital ICF for review and be scheduled for a video call for screening.
    - IF the subject meets all eligibility criteria + have doctor's referral note = Enrolled
    - IF the subject meets all eligibility criteria but do not have doctor's referral note = will be scheduled for **clinical interview** (15 minutes) with study PI
        - If MDD diagnosis is confirmed = enrolled

Screening

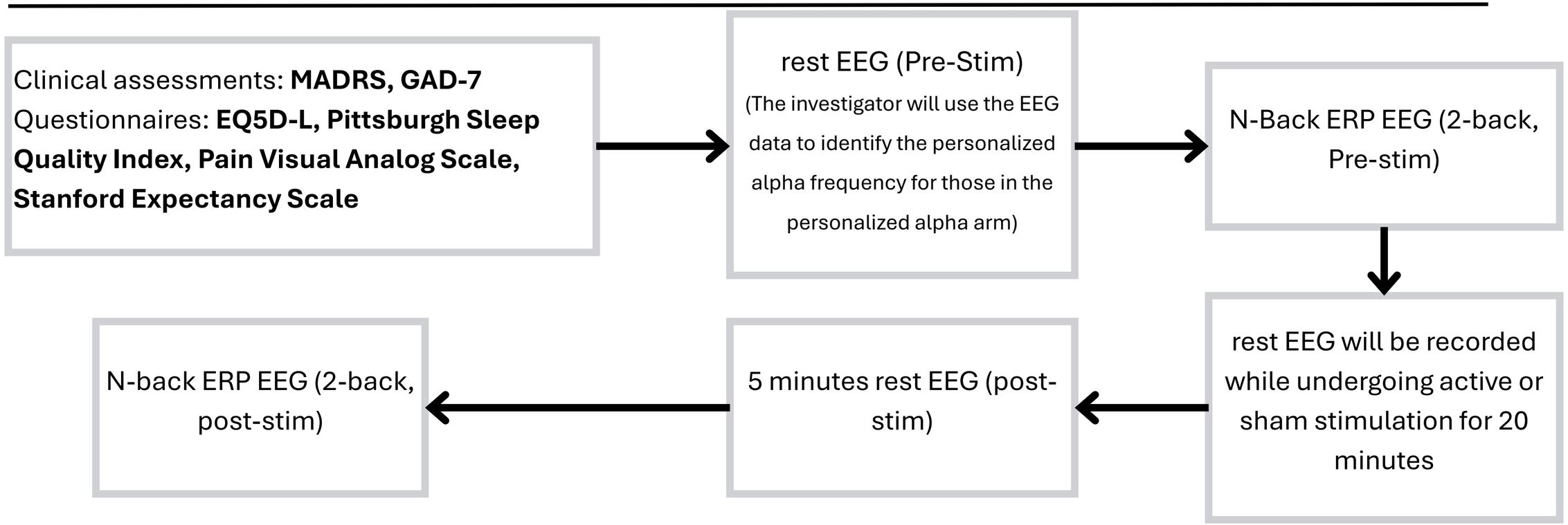
- The Sponsor research staff member will complete the screening CRF with the subject during the video call.
  - The following information will be gathered during screening via the Screening CRFs:
    - Demographics data
    - Inclusion/exclusion criteria checklist
    - Medical and psychiatric history
    - Current medications
    - Drug Abuse Screening Test (DAST-10) and Alcohol Use Disorder Identification Test (AUDIT)
    - MADRS

Randomization

- **Randomization** tables of a fixed size
  - By a research staff that are not involved in participant assessment
  - Using randomly permuted blocks into one of the three study arms:
    i. Personalized Neuro Rx Alpha Arm
    ii. Neuro Rx Gamma Arm
    iii. Sham Arm

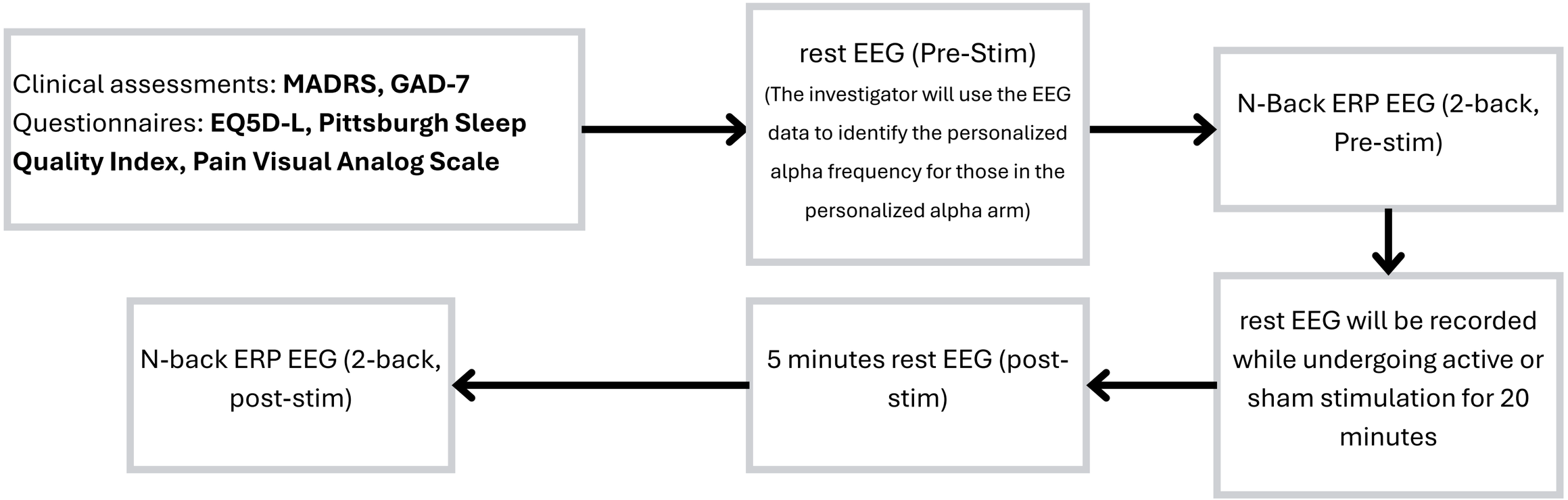
They will then be scheduled for their baseline visit.

Baseline Visit (V1)



- At the end of the baseline visit, sujects will be instructed on how to use the device and to contact staff in case of AEs. They will also be provided with a daily diary.
- They will be instructed to wear the device **daily for 20 minutes for 6 days per week.**

Follow-up visits (Week 2,4,8)



- Subjects will be sent reminder/follow-up emails three times a week to confirm that they are using the device and to follow-up regarding any adverse events.
- All procedures are identical to baseline but **NO reseting** of the device for Neuro Alpha RX group in week 8.

Week 12 Follow-up call

- Voluntary

- Subjects will be administered with the clinical assessments:
  - **MADRS**
  - **GAD-7**

Subject Withdrawal

- Subjects may be withdrawn for the following reasons:
    i. **Subject's choice to withdraw their consent to participate**
        1. If they withdraw before randomization = screening failure
        2. if they withdraw after randomization = will have any available data evaluated, up to the withdrawal time
    ii. I**nvestigator's choice to withdraw subject from the study**
        1. if withdrawal is before randomization = screening failure
    iii. Study termination for either administrative or safety reasons
- The investigator will complete the End of Study CRF upon subject withdrawal
- Participants will be withdrawal if they become pregnant

MEDICAL DEVICES

1. Medical Devices Overview
2. Device Components
3. Device Specification
4. Device Placement & Operation
5. Device Safety & Usability

Medical Devices Overview

Neuro RX Alpha & Neuro RX Gamma

- Gamma deliver NIR PBM to the brain, transcranially and intranasally
- Identical hardware
  - Only differ in frequency of PBM being delivered

Neuro RX Alpha	Personalized alpha frequency (7 - 13 Hz) Designed for individuals with alpha rhythm-related biomarkers
Neuro RX Gamma	Fixed gamma frequency (40 Hz) Targets gamma-related brain wave activity
Sham Device	Identical apperance but no active stimulation

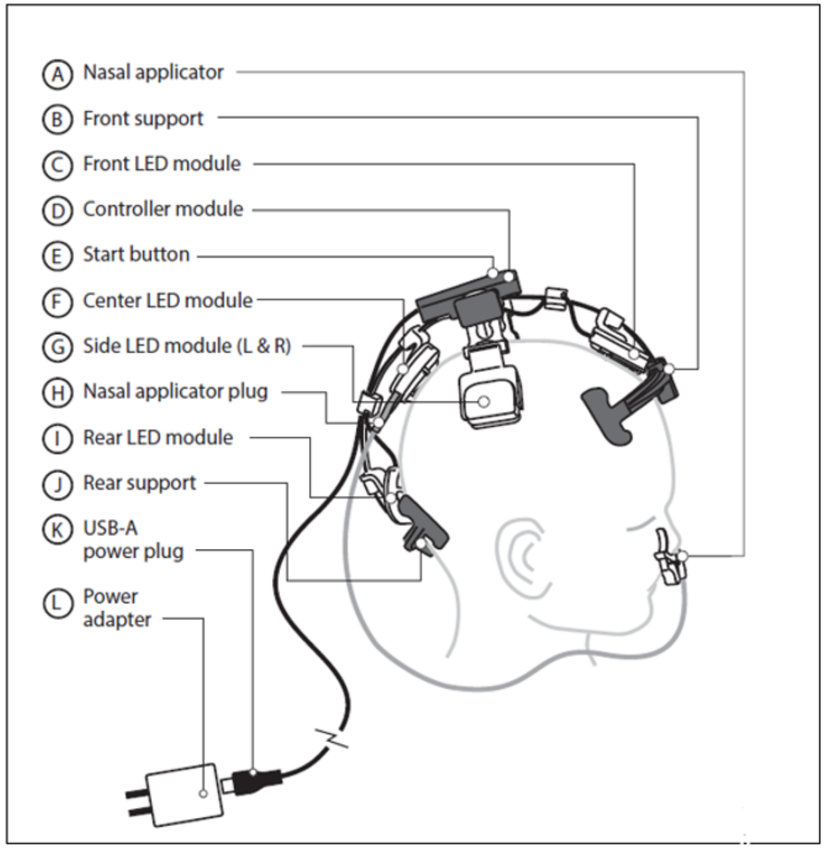
Device Components

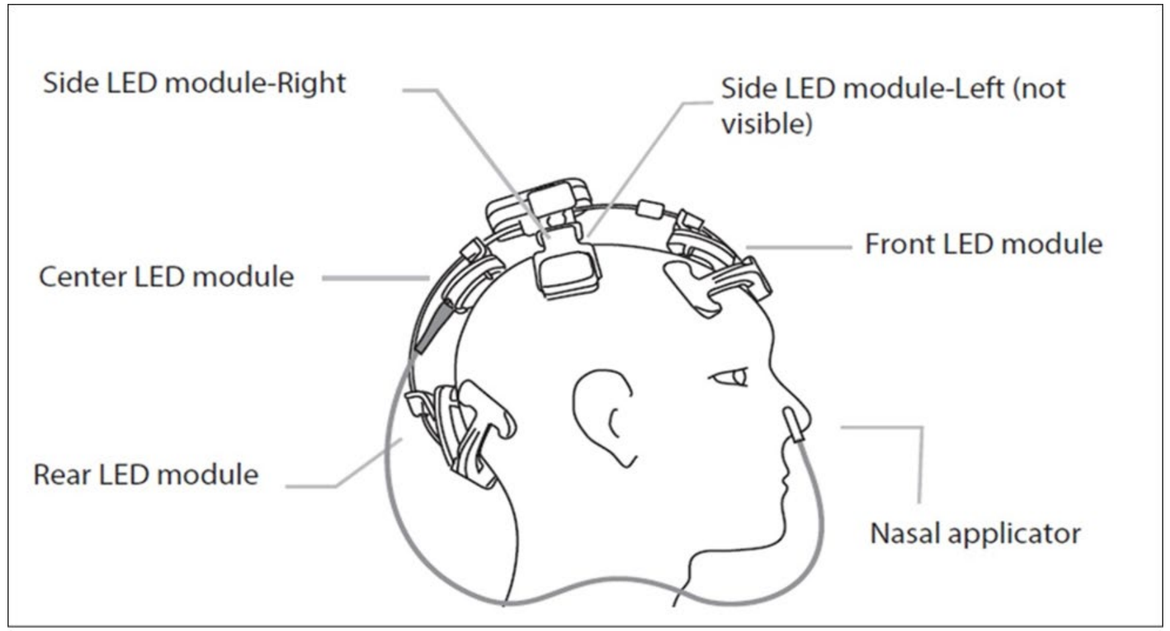
Component	Details
Headset	• 5 transcranial diodes placed over the skull • Positioned to target key brain regions • Built-in controller
Nasal Applicator	• 1 intranasal LED • Delivers 810 nm near-infrared light. • Designed for deep brain structure stimulation. • Includes secure clip for proper placement.

Power Supply	• Medical-Grade DC Adapter:
	  ◦ Voltage: 7.5 VDC.
	  ◦ Current: 1 Amp.

Session Features	• Preprogrammed 20-minute session with automatic shutoff at session complete

Device Components





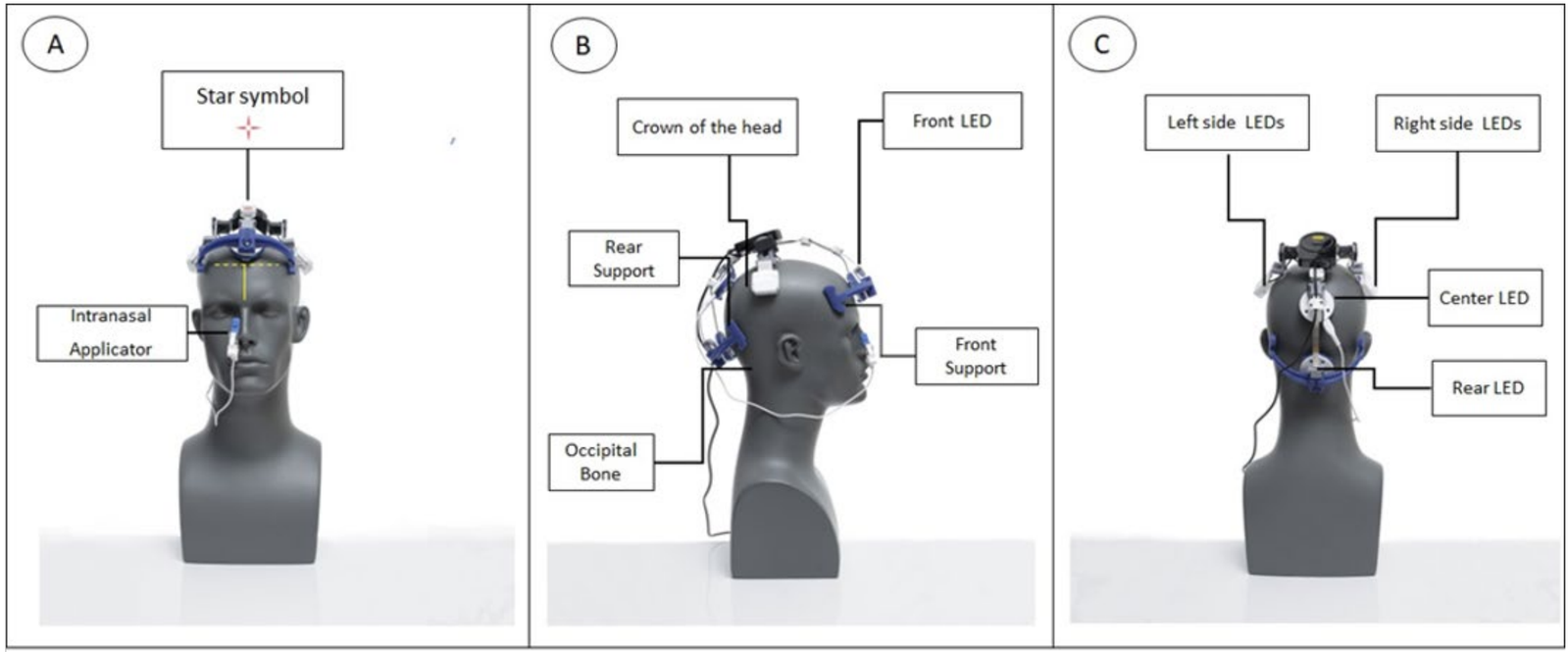
Device Specifications

Specification	Details
Wavelength	810 nm (Near-infrared light)
Power Density	Transcranial LEDs: 75–100 mW/cm^2. Intranasal LED: 25 mW/cm^2.
Total Energy Delivered	Transcranial: 255 J/session. Intranasal: 15 J/session.
Session Duration	20 minutes/session, 6 days/week, 1 rest day.

Device Placement

Headset Placement

- Transcranial LEDs:
  - Front LED: Positioned above the forehead (prefrontal cortex).
  - Lateral LEDs: Over angular gyri on both sides of the head.
  - Rear LED: Aligned with the occipital region.
  - Ensure the headset fits snugly but comfortably to maintain proper LED alignment.



Nasal Applicator Placement

- Intranasal LED:
  - Inserted into one nostril
  - Secure using the attached clip to avoid movement during the session

Device Procedures

1. **Start Session**
    a. Once the headset and nasal applicator have been positioned, must connect to electrical outlet
    b. Green light confirms the flow of electric current to the device
    c. Initiate the treatment by pressing the start button on the controller
2. **Session duration**
    a. The power indicator LED on the controller will flash green throughout the 20 minutes
3. **Post-session**
    a. Power indivator will stop flashing and the device will beep twice

Device Safety & Usability

No direct benefit to participants

- **Clinical Improvement:**
  - Potential reduction in depressive symptoms (MADRS scores).
- **Innovative Treatment:**
  - Non-invasive, adjunctive PBM
- **Scientific Contribution:**
  - Adds evidence to PBM efficacy for MDD
  - Explores personalized frequency optimization (alpha vs. gamma)

Device Calibration and Maintenance

- Calibration not required for the Alpha, Gamma and Sham devices
- Equipment is stored securely at room temperature in a controlled environment

Investigational Device Management

- **Device Inventory Log**
  - Includes the Serial number, the date assigned to a subject, date of first use and subject ID
  - Device will be given to subjects during the baseline visit
  - Subjects will be asked to return the device at the end of their week 8 visit
  - **Return**: If the Device is associated with a device-related adverse event, malfunction or failure, the Device should be returned to Vielight Inc. for appropriate action.

EQUIPMENTS

1. Study Specific Equipment
2. Other Equipment
3. Data analysis and collection software

Study-specific Equipment

- Neuro RX Alpha
- Neuro RX Gamma
- Sham Device

- Device Reprogrammer (alpha personalization)

- EEG System

Additional equipment

- Drop Box Software (HIPPA compliant)
- Hard drive? Or Electronic device storage? (Storage size to be decided)
- SPSS
- MatLab

STUDY-SPECIFIC SOP

1. Training & Documentation

2. Non-compliant Subjects

Training and Documentation

- All study staff must undergo training on the protocol and study-specific procedures to ensure consistent application and protocol adherence
- Any updates or amendments to the SOPs are communicated to all relevant staff and recorded appropriately.

Non-Compliant Subjects

- For participants who are noncompliant with follow up visits, every effort will be made to collect the data requested by this protocol through the follow up period.
- All data collected up until the period the subject has withdrawn from the study will be used for this study.
- A participant will be defined as non-compliant if they miss more than for consecutive days of treatment in a 6 day treatment period.

DATA COLLECTION

1. Good Documentation Practices
2. Source Documents
3. Case Report Forms (CRFs)
4. Data Storage and Protection

Good Documentation Practices

- All data must be legible, accurate, and complete.
- Corrections are made by drawing a single line through errors, writing the correct entry nearby, and dating/initialing the correction.
- Ensure adherence to ICH-GCP guidelines and study-specific SOPs for data documentation.

Source Documents

- All study-related participant information is recorded as source documents, including eligibility criteria and assessments.
- These documents must include signed consent forms, medical history, and clinical assessments.
- Records must be securely stored and accessible only to authorized study personnel.

Case Report Forms (CRFs)

- CRFs must be completed for each participant during study visits.
- The header on each CRF includes participant ID, initials, short study title, and protocol number, and visit date.
- Data must align with source documents for accuracy.
- Store completed CRFs in locked, secure storage (electronic or physical copy).
- CRFs are completed by qualified study staff who are appropriately trained.
- For participants who withdraw their consent for study participation, the Investigator will complete the “End of Study CRF” and no additional data will be collected after the date of their discontinuation.

Data Storage and Protection

- A Subject ID Log shall link the data collected during the study to source documents such as medical records.
- The Subject ID Log shall be kept securely and confidentially with access restricted to study staff.
- Subjects will remain de-identified throughout data collection and analysis.
- Data is stored on a secore electronic storage device ?

Sponsor Records

Trial Master File, including Protocol, ICF and any amendments
IRB Approval Letter and any amendments
Health Canada Investigational Testing Authorization and any amendments
All correspondence, including required reports
Signed investigator's agreements including financial disclosure information
Records and reports concerning adverse device effects and complaints

Device inventory Log	Records the serial number, date assigned to subject, date of first use, subject ID Maintained by research staff

Subject ID log (Enrolment Log)	Links data collected during the study to source documents will be kept securely on the drive

Required Documents from Investigator

Signed investigator Agreement	CV	IRB or other regulatory documents

Investigator Records

CRF	Includes: 1. Screening 2. Baseline 3. Week 2 4. Week 4 5. Week 8 6. Week 12 Follow up 7. End of Study CRF 8. Adverse Events CRF

Subjects medical history and case history

Deviation Log

INVESTIGATOR AND STUDY TEAM ROLES AND RESPONSIBILITIES

1. Sponsor Responsibilities
2. Investigator Responsibilities
3. Training Requirements
4. Delegation of Duties
5. Deviations and Amendments
6. Documentation and Reporting

Sponser Responsibilities

Vielight as the Sponser of the study is responsible for the following:

- Selecting qualified investigators
- Providing investigators with necessary information
- Providing appropriate training to all study personnel
- Selecting monitors qualified by training and experience
- Ensuring that the IRB approval is obtained
- Ensuring that Investigational Testing Authorization is obtained
- Ensuring that IRB or regulatory authority are informed of significant new information
- Providing the devices to qualified investigators
- Investigate unanticipated, device related AEs and report to IRB/Health Canada
- Obtaining signed Investigator Agreement for each investigator prior to their participation in the study
- Reporting per local regulations
- Retain records for at least 2 years following completion of this study.

Investigator Responsibilities

Responsibilities of the Investigator include, but are not limited to:

- Ensuring that all personnel are adequately informed and understand their trial-related duties and functions
- Obtain informed consents of subjects.
- Permit monitor to inspect facilities and records.
- Maintain medical histories of subjects.
- Enroll subjects, execute the study, transcribe data from source documents to case report forms, and conduct study in accordance with protocol.
- Submit annual progress reports, final reports, and Adverse Event reports to the IRB and to Sponsor.
- Notify the local or national authority and the manufacturer (Vielight Inc.) within 72 hours of any incident that meets the criteria
- The Investigator will allow direct access to source data/documents for trial related monitoring, audit, IRB review and regulatory inspection.

Training Requirements

- All study personnel must undergo training on the study protocol, device usage, and GCP guidelines.
- Training records are maintained in the Investigator Site Binder (ISB) and on shared network drives.
- Any updates to procedures or amendments are communicated and documented promptly

Delegation of Duties

- The PI delegates study-related activities to qualified team members, as documented in the Delegation of Authority Log.
- Tasks include participant enrollment, data collection, device operation, and reporting of deviations or adverse events.
- All staff listed in the delegation log must be trained and authorized

Deviations and Amendments

- Deviations from protocol must be reported to the sponsor within a reasonable timeframe.
- Subject-specific deviations are documented in the Deviations Log.
- Non-subject-specific deviations (e.g., unauthorized device use) are reported to the PI.
- All deviations are subject to IRB reporting requirements

Documentation and Reporting

The investigator must maintain complete and accurate records, including:

- Correspondence with the sponsor, IRB, and regulatory authorities.
- Case report forms, consent forms, and medical histories.
- Adverse event reports and follow-up data.
- Documentation of protocol deviations and the reasons for changes

SAFETY & ADVERSE EVENTS

1. Criteria for determining Reportability
2. Reporting AEs and Device Incidents
3. Anticipated AEs

Adverse Events

- Participants will be asked to report any adverse events in a daily basis through their daily diary and to contact research staff in the case of device-related adverse events.
- Study staff will record the characteristics of each adverse event on an **Adverse Event CRF**.
- The Investigator will judge each adverse event as to its relationship and level of relatedness to the investigational device.

Relatedness will be scored consistent with CTCAE v4.0 guidelines.

- **Unrelated**
- **Unlikely**
- **Possible**
- **Probable**
- **Definite**

Device attributable Adverse Events

- Adverse event (AE) terminology reporting will be standardized using medical dictionary for regulatory activities (MeDRA)
- Aes will be coded by system organ class or SO
- Separate tables will be provided for all adverse events, Grade 3-5 adverse events, serious adverse events, and serious treatment-related adverse events.

Adverse Events

- Besides Relatedness, the Investigator will identify the **date of onset** , **severity** , and **duration** of AEs
- **Severity** is determined from the grades presented in CTCAE v4.
  - **Grade 1** – Mild AE
  - **Grade 2** – Moderate AE
  - **Grade 3** – Severe AE
  - **Grade 4** – Life-threatening or disabling AE
  - **Grade 5** – Death related to AE

- All adverse events will be monitored until they are adequately resolved or explained.

Reporting Adverse Events & Device Incidents

- All Serious Adverse Events must be reported to the study Sponsor immediately, not to exceed 24 hours after the investigator first learns of the event
  - The complete adverse event investigation form shall be faxed or emailed to the sponser within 24 hours with a cover letter describing the event, detailed medical history, concomitant medications, and assessment of compliance with therapy
- All adverse events, serious or non-serious adverse events will be recorded reported in the daily diary.
- All SAEs need to be followed until the event is resolved (with or without sequelae).
  - In case of death, all possible information that is available, including the possible relationship to the device, should be provided.
- The investigator must submit to the Sponsor any unanticipated adverse device incident (see Definitions) within 24 hours
  - Must also report to IRB using study's subject identifier
- Sponsor will be responsible for submitting incident information to Health Canada within the specified timeframe.

Anticipated Adverse Events

- The study devices have the potential to cause nosebleeds, redness or irritation of the nostril.
- For individuals that are prone to nose bleeds, the intranasal diode (light piece) may trigger a nosebleed.

MONITORING AND AUDITS

1. Monitoring Purpose and Activities
2. Auditing Procedures

Monitoring Purpose and Activities

1. **Purpose of Monitoring**
   - Ensure adherence to protocol, GCP, and regulatory standards.
   - Verify data accuracy and participant safety.

2. **Monitoring Activities**
   - Regular review of data collected during study visits, including CRFs
   - Confirmation of adherence to study protocol and procedures.

Auditing Procedures

Definition: "An audit is a systematic and independent examination of trial-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported according to the protocol, SOPs, GCP, and applicable regulatory requirements".

Audit Responsibilities:

1. The Sponsor's Research Managers conduct audits to ensure protocol compliance.
    1. Dr. Genane Loheswaran & Dr. Janine Liburd
2. Key focus areas include investigator adherence to trial requirements, device accountability, proper documentation of protocol deviations and correct completion of CRFS and ICFs.

Documentation: All monitoring and auditing activities must be documented, including the date, findings, and any corrective actions implemented. Records are stored for a minimum of two years following study completion.

Discussion Q&A

1. Electronic data storage – Amazon
    1. Also include the training records

2. Get binders
    1. Hard copy of the trial master file
        1. With training records
3. Print CRFs