# PHYSIOLOGICAL CORRELATES OF ACTIVE MUSIC-MAKING AND PASSIVE LISTENING IN MUSIC BASED INTERVENTIONS

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# PHYSIOLOGICAL CORRELATES OF ACTIVE MUSIC-MAKING AND PASSIVE LISTENING IN MUSIC BASED INTERVENTIONS

A pilot, randomized, unblinded study of the effects of active participation in music making on stress hormones and heart rate variability with a passive listening control

**Funding Mechanism:**

**Principal Investigator:** *Flavio Frohlich, PhD*

**Co-Investigator:** *Dorita Berger, PhD, MT-VC, LCAT*

**Protocol Number:**

**Version Number:** *1.0*

**Date:** *12/14/17*

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## STUDY SUMMARY

| | |
|---|---|
| **Title** | *Physiological correlates of active music making and passive listening in music based interventions* |
| **Short Title** | *Correlates of active music making* |
| **Protocol Number** | |
| **Phase** | *Pilot study* |
| **Methodology** | *Within participants* |
| **Study Duration** | *2 sessions per participant, 1 hour* |
| **Study Center(s)** | *This is a single-site study performed at The University of North Carolina at Chapel Hill.* |
| **Objectives** (Purpose) | *Understand how active music making influences correlates of the HPA axis and ANS* |
| **Number of Subjects** | *20* |
| **Diagnosis and Main Inclusion Criteria** | *18-34, non musician, healthy controls* |
| **Description of Intervention** (Procedures/methods) | *Participants will recive a 40 minute music based intervention or will receive a listening control. Physiological measure will be taken before and after the intervention/control* |
| **Related IRB Applications** | |

# 1 KEY ROLES

## 1.1 INDIVIDUALS

**Principal Investigator** Flavio Frohlich, PhD

**Co-Investigator** Dori Berger, PhD, MT-BC, LCAT

## 1.2 INSTITUTIONS

The University of North Carolina at Chapel Hill

## 1.3 OPTIONAL

IRB
The University of North Carolina – Chapel Hill
Medical School Building 52
Mason Farm Road
CB #7097
Chapel Hill, NC 27599-7097
(919) 966-3113

## 1.4 FUNDING SOURCES

Please list below the funding sources for this project

| Sponsor Name | UNC Ramses Number | Sponsor Type | Prime Sponsor Name | Prime Sponsor Type | Sponsor/Grant Number |
|---|---|---|---|---|---|
| | | | | | |

**External Funding**: This project is externally funded but UNC-CH is not the direct recipient of federal funds.

**UNC-CH Funding**: This project is not funded through UNC-CH.

**Classified**: This project is not classified.

# 2 INTRODUCTION

This document is a protocol for a human research study. This study is to be conducted according to U.S. and international standards of Good Clinical Practice (FDA Title 21 Part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

## 2.1 BACKGROUND

Major depressive disorder (MDD) is the leading cause of disability for U.S. citizens aged 15-44, and affects more than 16 million Americans each year. Existing interventions struggle to combat this societal burden and fail to reach the large number of treatment resistant patients, creating an urgent need for the development of new treatment paradigms. Hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis and dysregulation of the autonomic nervous system (ANS) have been implicated in MDD. Listening to music alters stress hormone levels and heart rate variability (HRV), physiological correlates of the HPA axis and ANS respectively. Active music-making's effects on these correlates has yet to be studied. Since active musical engagement involves multiple sensory inputs—proprioceptive and motor in addition to auditory—it has the potential to heighten physiological changes associated with listening to music alone. By contrasting a structured participation MT intervention with a listening control, we will target the effects active participation in music-making as a potential treatment for MDD.

## 2.2 INVESTIGATIONAL AGENT

Our investigational agent is music. In intervention sessions, participants will be working one on one with a music therapist, participating in musical activities. In control sessions participants will be listening to musical excerpts.

## 2.3 STUDY AIMS/HYPOTHESES

### 2.4.1 PRIMARY OBJECTIVE

We hypothesize that both conditions will produce a decrease in stress hormone levels and LF/HF, and an increase in HF. We also expect these changes to be greater in the active MT intervention than the passive listening condition. This would demonstrate the interventions ability to uniquely target the HPA axis and ANS, relaxing the participant.

# 3 SUBJECT SELECTION AND WITHDRAWAL

A total of 20 participants will be recruited for this study and all data will be collected at UNC-CH. No specific plans have been made to enroll participants from vulnerable populations.

## 3.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, a participant must meet all of the following criteria:

- 18-34 year olds.
- Capacity to understand all relevant risks and potential benefits of the study (informed consent)
- Willing to comply with all study procedures and be available for the duration of the study
- Speak and understand English

## 3.2 EXCLUSION CRITERIA

A potential participant who meets any of the following criteria will be excluded from participation in the study

- Formal musical training—more than three years of musical training before the age of 12 and any after this age.
- Outside age range
- Non-English speaker
- Cardiovascular disease/medications
- Neurological disease/medications

- Anything that, in the opinion of the investigator, would place the participant at increased risk or preclude the participant's full compliance with or completion of the study

**Justifications for any exclusions based on race, gender, or ethnicity:** Non-English speaking individuals are excluded because the ability to accurately and completely communicate study information, answer questions about the study, and obtain consent are necessary.

**Justification for exclusions based on formal musical training:** Musical training would predispose individuals to interact with an isochronous auditory stimulus in a different way than non-musicians. Their ability to entrain and coordinate with the pulse will likely be better as they have spent significant amounts of time entraining to rhythms through musical performance and instruction.

**Justification for exclusions based on cardiovascular disease:** Cardiovascular disease would likely influence the ANS measures we would be recording in the study (HR, HVR) making our results not representative of healthy individuals. This pilot study is not meant to assess clinical outcomes of the entrainment task.

**Justification for exclusions based on neurological diseases and CNS disorder medication:** Neurological diseases would likely influence the behavior and cognitive processes of the participants, affecting their entrainment ability, making our results not representative of healthy individuals. This pilot study is not meant to assess clinical outcomes of the entrainment task.

## 3.3 STRATEGIES FOR RECRUITMENT AND RETENTION

### 3.3.1 RECRUITMENT

Fliers will be designed to recruit participants that meet our inclusion criteria, and will be posted around campus in locations where undergraduates are likely to see them. Campus emailing-lists will also be used to distribute study information and inclusion criteria to recruit individuals. Individuals will self-identify and email us, at which point we will call them for a telephone screening.

### 3.3.2 RETENTION

Subjects will receive the full $10.00 immediately at the conclusion of both the first and second visit. If a subject withdraws from participation in the middle of their visit after the fitting of EKG electrodes, full compensation will still be awarded. Each research staff member will be easily available for the participants to contact via email or phone.

The inclusion criteria state that each participant must be able to understand all risks and benefits associated with this study. We will be asking each participant to answer questions about the consent form to determine that the study process and the duration of participation are completely understood by all participants. The study team will work hard at forming a professional relationship with each participant so that they feel comfortable and willing to discuss what may be sensitive information.

# 4 BASIC STUDY DESIGN

**Figure 1.**


A within participants design will be used, where each participant receives the active intervention and the

passive control separately.

In the active intervention, participants will undergo a 40 minute structured MT intervention that includes standardized breathing, rhythmic, and improvisational exercises. In the passive control, participants will listen to 40 minutes of clinician selected music, matched in style and structure to the segments of the intervention.

Participants will be fitted with EKG electrodes and 5 minute HRV baseline recordings will be taken, during which the participants will be given unrelated reading material to keep them alert and control behavior. Stress hormones—cortisol and alpha-amylase—will be assessed though saliva samples taken from the participant. Attention, handedness, and musical experience questions will be administered to collect supplementary data that can account for and justify the exclusion of outliers.

### 4.1 TREATMENT ASSIGNMENT PROCEDURES

The treatment order will be randomized and counter balanced. Participants will be randomly sorted into either intervention first or control first conditions.

#### 4.1.1 RANDOMIZATION PROCEDURES

Trials types will be randomly dispersed throughout an experimental block, and block design will be automated and randomized in Matlab.

## 5 STUDY SCHEDULE

It is important to note that consent, scales, and experiments will all take place in a private room. Any phone calls will take place in a private lab environment as well.

### 5.1 SCREENING

Telephone screening will take place before the first session to ensure the participant is eligible to participant and to schedule a session time.

### 5.2 SESSIONS

Upon arrival for the first session participants will look over and sign a consent form. They will then complete initial attention and handedness questionnaires, followed by a baseline HRV recording and collection of initial saliva samples. Then either the intervention or the control will be administered, followed by another HRV baseline recording and collection of saliva samples. After this, participants will be allowed to leave. Total participation time will be 1 hour and participants will be compensated $10 upon the completion of each session. In session 2 participants will go through the same procedure, but will receive the opposite treatment condition, and will not complete the handedness questionnaire a second time. A week will pass before the participant can come back for their second session. Sessions will be held in UNC's Keenan Music Building. We have previously conducted studies here, working closely with the music department to secure equipment, storage space, and study locations.

## 6 STUDY PROCEDURES/EVALUATIONS

### 6.1 SELF-REPORT MEASURES

A. *Attention questionnaire*—assess the arousal and engagement of the participant at the beginning of each session
B. *Handedness questionnaire*—assess whether the participant is right handed or left handed
C. *Musical experience questionnaire*—assess the participant's past musical experience as well as any thoughts or concerns they may have had about the treatments

### 6.2 SPECIAL ASSAYS OR PROCEDURES

A. *4 HRV recordings*—2 per session, recorded though disposable EKG electrodes
B. *4 saliva samples*—2 per session, recorded though oral collection swabs

## 7 STUDY INVESTIGATIONAL PRODUCT

### 7.1 ASSESSMENT OF PARTICIPANT COMPLIANCE WITH STUDY INVESTIGATIONAL PRODUCT

Compliance for this study includes attending the entire experimental sessions and following the instructions given by the experimenter. Non-compliant participants will be asked to leave, will not be payed, and the experimental data will be discarded.

## 8 POTENTIAL RISKS AND BENIFITSPotential Risks and Benefits

### 8.1 BENEFITS TO SUBJECTS AND SOCIETY

Music based interventions (MT) are a cost-effective, accessible, and holistic treatment option with social, rhythmic, creative, sensorimotor, and respiratory components, giving it the potential to improve the quality of life for a diverse array of disorders. Despite this, the literature surrounding MT is controversial due to the lack of standardization in clinical and research practice. Interventions range in composition from passive listening of participant selected music to clinician lead improvisational sessions. This inhibits a mechanistic understanding of how MT functions, and what components produce therapeutic effects. Controlled studies that target physiological outcomes are vital for the development of evidence based MT treatments.

### 8.2 POTENTIAL RISKS

#### 8.2.1 PSYCHOLOGICAL

**Risk of Confidentiality Breach**:

In the unlikely event of a breach of confidentiality, people might discover that an individual was involved in this research study. This is especially sensitive because the clinical population used for this study may be subjected to negative consequences caused by the stigma of mental disorders. Furthermore, some might not agree with the principle of participating in research or of changing natural brain activity. To avoid breaches in confidentiality, study documents that contain personal information, including the informed consent, and the document that links study ID numbers to personal identifying information are kept in locked filing cabinets in locked rooms, separate from any source documents containing participating dummy identifiers. All data is stored in locked cabinets inside locked offices; electronic data will be stored only on password-protected computers, and data encryption methods will be used during communication between investigators. Only study personnel will have access to these data. All study staff participate in annual

human participating training that includes education about responsibilities to minimize the risk of confidentiality breach.

# 9 DATA AND SAFETY MONITORING

## 9.1 FROHLICH LAB MONITORING PLAN

The purpose of this monitoring plan is to present the Frohlich Lab's approach to monitoring clinical trials. The plan facilitates compliance with good clinical practice (GCP):

a. The rights and well-being of human subjects are protected.
b. The reported trial data are accurate, complete, and verifiable from source documents
c. The conduct of the trial is in compliance with the currently approved protocol/amendment(s) with GCP, and with applicable regulatory requirement(s)

This section identifies key monitoring activities and specifies the data to be reviewed over the course of a clinical trial. This is a single site, investigator-initiated, clinical trial, so there will be no site monitoring plan in place.

The latest version of the approved IRB application for this clinical trial will be followed at all times. This responsibility falls into the hands of the study coordinator and research assistants. If at any time there is a deviation from protocol, the deviation from protocol log will be filled out. All team members will be trained on how and when to use this log. The most up-to-date IRB application will be on file in the Clinical Trials office in Room 233 of the Medical School Wing C. Deviations will be sent to the IRB every 4-6 weeks (if necessary).

Periodically, study staff should review 3 randomly selected inform consent forms to ensure that (1) these forms have been filled out appropriately, and (2) the consent form process was followed and properly documented. Should any consent form be in violation, the research team will perform and document a complete review of all consent forms.

## 9.2 EARLY WITHDRAWAL OF PARTICIPANTS

### 9.2.1 REASONS FOR WITHDRAWAL

A study participant will be discontinued from further participation if:

- The participant meets any exclusion criteria (either newly developed or not previously recognized).
- Failure to comply with instructions
- No show on study dates
- Request by subject
- Anything that, in the opinion of the investigator, would place the participant at increased risk or preclude the participant's full compliance with or completion of the study.

Participants are free to withdraw from participation in the study at any time upon request.

# 10 SAFETY & REPORTING

It is important to assess safety over the course of this study. This section describes in detail how safety is assessed, reporting of Adverse Events, Serious Adverse Events, and Unanticipated Problems. This section is a reference for internal use.

## 10.1 METHODS AND TIMING FOR ASSESSING, RECORDING, AND ANALYZING SAFETY PARAMETERS

### 10.1.1 UNANTICIPATED PROBLEMS

Unexpected Events (UE) will be recorded on the UE/SAE log (Appendix D) and will include information such as the date of the event, when the study team was informed of this event, details of the event, when the IRB was notified, and whether the SAE form was completed. The IRB will be notified of each UE that may occur during the study.

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research (in the guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

If an UE occurs the IRB will be notified and the study will be adjusted as needed to protect the health and safety of the participants. Depending on the nature of the UE, the research protocol, inclusion/exclusion criteria, and informed consent will be changed to reflect the possibility of this event reoccurring. During this time, no new participants will be recruited and the research procedures for currently enrolled participants will be stopped. Each UE will be recorded and reported throughout the study.

## 10.2 REPORTING PROCEDURES

We will be adopting the following table for reporting procedures:

| **What Event is Reported** | **When is Event Reported** | **By Whom the Event is Reported** | **To Whom the Event is Reported** |
|---|---|---|---|
| Fatal or life-threatening unexpected, suspected serious adverse reactions | Within **24 hours** of initial receipt of information | Investigator | Local/internal IRBs |

| | | | |
|---|---|---|---|
| Non-fatal, non-life threatening unexpected, suspected serious adverse reactions | Within **48 hours** of initial receipt of information | Study Coordinator | Local/internal IRBs/Institutional Officials, |
| Unanticipated adverse device effects | Within **10 working days** of investigator first learning of effect | Investigator | Local/internal IRBs |
| Unanticipated problem that is not an SAE | Within **7 days** of the investigator becoming aware of the problem | Investigator | Local/internal IRBs/Institutional officials |
| All Unanticipated Problems | Within **30 days** of the IRB's receipt of the report of the UP from the investigator | IRB | OHRP |
| | | Investigator | External IRBs |

### 10.3 TYPES AND DURATION OF FOLLOW-UP OF PARTICIPANTS AFTER ADVERSE EVENTS

Co-I will follow up with participants within one week of an AE.

## 11 STATISTICAL PLAN

### 11.1 STATISTICAL ANALYSIS STRATEGIES

HRV recordings will be analyzed for high frequency (HF) and low frequency (LF) components which can be used to assess the relative activation of the ANS. The HF component corresponds with parasympathetic activation, where as the LF component divided by the HF component corresponds with sympathetic activation. Saliva samples will be sent to and tested by Salimetrics to calculate hormone levels.

Post treatment HRV components and hormone test results will be compared to pre treatment baselines through a treatment group (active intervention, passive control) × time (pre treatment, post treatment) repeated measures ANOVA. The results we produce will allow us to estimate the target effect size, power, and sample size necessary for a future clinical trial that uses the intervention to treat MDD.

### 11.2 SAMPLE SIZE DETERMINATION

This clinical trial represents a pilot study. A pilot study is a clinical trial that is conducted to decide whether a new treatment should be tested in a large controlled trial; therefore, we do not calculate sample size. This study can be considered a pilot study, as it is the first time this specific treatment will be performed on this clinical population. The results from this study will be used to determine sample sizes for future, large-scale clinical trials. In addition, we have to restrict the number of included participants to a small sample size due to limited funding resources.

### 11.3 DATA MANAGEMENT

Data will be stored in a password-protected cloud-based data system that does not contain any patient information. Individual records are referred to by dummy identifiers that cannot be traced back to the study participants except with the master code list that is stored separately in a secured location.

# 12 DATA HANDLING AND RECORD KEEPING

The study coordinator and research assistants ae responsible for the accuracy, completeness, legibility, and timeliness of the data reported.

## 12.1 PHI AND HIPAA

Information about study participants will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from the participants in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a participant revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of participant authorization. For participants that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the subject is alive) at the end of their scheduled study period.

## 12.2 CONFIDENTIALITY

To ensure confidentiality, all data will only be referenced by a dummy identifier. Source documents (i.e. paper forms) will be kept in a locked file cabinet in a locked office. In addition, all data will be stored on a password-protected computer using a password-protected data collection tool (REDCap). The key linking dummy identifiers with participant information will be securely located separate from all other data collected.

### 12.2.1 ACCESS TO SOURCE DOCUMENTS

The research coordinator, research assistants, and PI will have access to all of the source documents collected over the course of the study. The Co-I and medical monitor will have access to files upon request, as they will need access to the locked rooms and filing cabinets in which these documents are located.

Data will stay on a password-protected computer. Subsequently, a copy will be processed on a separate, password-protected desktop computer in the Frohlich Lab (Neuroscience Research Building 4129).

### 12.2.2 SENSITIVE INFORMATION

No sensitive information will be collected. Some potentially sensitive medical questions will be asked for screening purposes—such as “Do you suffer from cardiovascular disease?”—but dummy identifiers will be used to mask sensitive information.

### 12.2.3 OTHER

Please note that there is no significant risk of deductive disclosure in this study. In addition, none of the groupings or subgroupings used in analysis will be small enough to allow individuals to be identified.

## 12.3 SOURCE DOCUMENTS

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Source data include:

**PARTNERS HUMAN RESEARCH COMMITTEE (IRB).**

- All IRB correspondences are documented
- The study staff is IRB approved prior to performing any study procedures
- Adverse events and deviations are reported to the IRB per current guidelines and stored appropriately
- All versions of the IRB protocols and informed consent forms are on file

**INFORMED CONSENT.**

- Ensure that participant identification is not recorded on the ICF (i.e., no participant ID)
- There is documentation that the participant is given a copy of the consent form
- The participant and study representative signed and dated the consent form for him/herself
- The participant initialed and dated all appropriate pages on the informed consent form
- Note to file (Appendix F) made for any informed consent deviations
- Ensure a valid (current version date) copy of the consent form was used

**PROTOCOL DEVIATIONS.**

- Any and all protocol deviations (exceptions and violations) are documented in the participant folder and reported to the IRB as required

**OTHER SOURCE DOCUMENTS.**

- Each participant folder will contain a checklist to ensure that all source documents are administered and collected properly. The checklist will be dated by the researcher for each time an assessment is administered
- Review participant folders to ensure the accuracy, completeness, and legibility of the data.
- Any correction made to the source documents is dated, initialed, and explained. The original entry should not be obscured.
- The protocol-specific source documents are on file.
- Source documents are completed in ink.
- Note to files (Appendix F) are made for missing or incomplete data and to explain any discrepancies or additional comments.

**DNA.**

- Participant names will not be on any of the samples collected. DNA is sequenced to check for one nucleotide. When testing is performed, only de-identified information is shared with an outside party. This information will not be shared with anyone outside of the study personnel, including the participant.

## 12.4 DATA MANAGEMENT RESPONSIBILITIES

The responsibilities designated to each member of the research team are documented on the Delegation of Authority Form. The study coordinator and research assistants will be responsible for the informed consent process, review for eligibility, questionnaire administration, data entry, device administration, EEG administration, and CRF entries. The study coordinator will be responsible for AE/SAE documentation and reporting, while the PI will be responsible for the AE assessment, review of the AE documentation forms, and overview of the research staff.

### 12.6 PROTOCOL DEVIATIONS

All deviations from the protocol will be addressed in study participant source documents. The researcher will complete a Protocol Deviation Log using the participant code as the identifier. This form will collect information such as the date the deviation occurred, details of what the deviation consisted of, any corrective and preventative actions that were taken as a result of the deviation, and the date that the PI and IRB were notified. The PI will review the information and initial once approved. A completed copy of the Protocol Deviation Form will be maintained in the regulatory file, as well as in the participant's source document. Protocol deviations will be sent to the IRB per their guidelines. The site PI/study staff will be responsible for knowing and adhering to their IRB requirements.

### 12.7 RECORD RETENTION

According to the University of North Carolina at Chapel Hill's Archives and Record Management Services schedule for General Records Retention and Disposition Schedule 6.10, records will be kept for 5 years after the completion of the study or grant end date, whichever is later.

## 13 ETHICAL CONSIDERATIONS

### 13.1 ETHICAL STANDARD

The investigator will ensure that this study is conducted in full conformity with the principles set forth in the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6; 62 Federal Regulations 25691 (1997).

### 13.2 INSTITUTIONAL REVIEW BOARD (IRB)

The Office of Human Research Ethics is responsible for ethical and regulatory oversight of research at UNC-Chapel Hill that involves human participants. The OHRE administers, supports, and guides the work of the Institutional Review Boards and all related activities. Any research involving human participants proposed by faculty, staff, or students must be reviewed and approved by an IRB before research may begin, and before related grants may be funded. OHRE and the IRBs are critical components of the coordinated Human Research Protection Program, which serves to protect the rights and welfare of human participants. All components of this program must work together to ensure institutional compliance with ethical principles and regulatory requirements. The following is a mission statement for the coordinated Human Research Protection Program:

The University of North Carolina at Chapel Hill is committed to expanding and disseminating knowledge for the benefit of the people of North Carolina and the world. An important part of that commitment to knowledge is research of the highest quality on all aspects of the health and behavior of people, and such research is only possible through the participation of humans as research participants. Human participants are partners in research and a precious resource to the university. At UNC-Chapel Hill, human participant research is a privilege, but not a right. Consistent with that philosophy, it is the mission of the UNC-Chapel Hill Human Research Protection Program to ensure that:

a. The rights and welfare of human participants are paramount in the research process;
b. The highest standards of ethical conduct are employed in all research involving human participants;
c. Research investigators are properly trained in the ethical and regulatory aspects of research with human participants;
d. Research investigators deal honestly and fairly with human participants, informing them fully of procedures to be followed, and the risks and benefits of participating in research; and

e. Research using human participants at UNC-CH conforms to applicable local, state, and federal laws and regulations and the policies of the university.

## 13.3 INFORMED CONSENT PROCESS

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of tACS will be provided to the participants and their families. Consent forms describing, in detail, the study intervention, device, procedures, and risks are given to the participant and written documentation of informed consent is required prior to the administration of any treatment or assessments used in this study. All consent forms will be IRB-approved and updated with any new information as modifications are made throughout the study.

Together, the researcher and potential participants will review the clinical trial in its entirety by reviewing the consent form together in a private location. At several intervals during the consent review, the researcher will ask the participant questions that will assess the comprehension of the information in the consent. If the participant is unsure or does not know, the researcher will return to that section and more carefully explain the information. Participants must sign the informed consent document prior to any procedures taking place. If needed, the participants will have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. Participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

## 13.4 EXCLUSION OF WOMEN, MINORITIES, AND CHILDREN (SPECIAL POPULATIONS)

Special populations will not be excluded.

## 13.5 PARTICIPANT CONFIDENTIALITY

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the research team. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants.

All data will only be referenced by dummy identifier code. Data will be stored on a password protected computer. A key connecting names and code numbers will be kept in a locked cabinet, accessible only by research personnel. All data will be stored and analyzed on password protected computers, also only accessible by research personnel. Participants will not be identified in any report or publication about this study. See *10 Data Handling and Record Keeping* for more information on source documentation storage and security.

## 13.6 STUDY DISCONTINUATION

In the event that the study is discontinued, participants who have completed or who are still enrolled in the study will be notified. Any new information gained during the course of the study that might affect participant's willingness to continue will be communicated within 2 days of the PI learning this information.

## APPENDIX: AE REPORT FORM

**Adverse Effects Report:**

*Reasons for Report (adverse event, time, date and place of occurrence if available)*:

1. What do we already know about the therapy?
    a.
2. What is the temporal relationship of the AE to the study therapy?
    a.
3. Does the AE improve or disappear when the therapy is stopped?
    a.
4. Is the AE a worsening of baseline symptom(s)?
    a.
5. Is the AE a result of an underlying concurrent medical condition(s) or concurrent medication(s)?
    a.
6. Additional Information provided by research team
    a.

Research team member signature _____

Date_____

Co-Investigator:

_____

_____

_____

_____

_____

_____

Steps to be taken (if applicable)

_____

_____

_____

_____

_____

Co-I signature

_____Date_____

PI Comments:

_____

_____

_____

_____
_____
_____

Steps to be taken (if applicable)

_____
_____
_____
_____
_____

PI signature

_____Date_____