Study Protocol and Statistical Analysis Plan for R21 AG076377: Testing the Efficacy and Mechanisms of an Adapted Resilience Building Intervention in People Aging With HIV (RISE+)

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Sponsor: NIA

National Clinical Trial (NCT) Identified Number: NCT05314088

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Table of Contents

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and applicable United States (US) Code of Federal Regulations (CFR). The Principal Investigator will assure that no deviation from, or changes to, the protocol will take place without prior documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial subjects. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the local Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from subjects who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Testing the Efficacy and Mechanisms of an Adapted Resilience Building Intervention in People Aging With HIV (RISE+)
Study Description:	This study is a pilot clinical trial examining the feasibility and efficacy of a resilience intervention among middle aged and older people with HIV.
Objectives:	To test the feasibility and efficacy of a resilience intervention among middle aged and older people with HIV
Endpoints:	Immediately after the 1 month after intervention, and 3 months after
Study Population:	People with HIV aged 45 and older
Phase:	N/A
Description of Study Intervention:	Four small group sessions one time per week for four weeks. Intervention includes psychoeducational videos and written activities on topics such as coping strategies, cognitive appraisals, the responsibility model, and social connections, all integrated into the overarching process of resilience.
Study Duration:	The R21 was 2 years with a 1 year NCE. Participants were recruited between 03/2023 and 05/2025 and final data collection ended in October 2025.
Subject Duration:	~5 months from baseline to 3 month followup

1.2 SCHEDULE OF ACTIVITIES (SOA)

2 INTRODUCTION

2.1 STUDY RATIONALE

This pilot clinical trial examined the feasibility and efficacy of a theory-driven resilience intervention that has been adapted for older PLHIV.

2.2 BACKGROUND

Despite evidence that: 1) older people living with HIV (PLHIV) experience a high burden of stress that is associated with myriad poorer outcomes, 2) psychological resilience may buffer the negative effects of stress in older PLHIV, and 3) older PLHIV may possess lower levels of this protective factor than seronegative counterparts, little work has examined strategies to bolster resilience in older PLHIV.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Risks associated with this study are minimal and involve only the amount of risk one would encounter in daily life, with the exception of the low risks associated with breach of data security and loss confidentiality, psychological distress that may be identified in the study via our depressive symptoms measures or spontaneously reported, and risks associated with the venipuncture (discomfort at injection site; small risk of local hematoma or infection; on rare occasions, drawing blood can cause dizziness, presyncope, and syncope). Note that blood draws will not occur for all participants, as many will have recent HIV clinic data that we can extract. We only anticipate that <30% of participants will require a blood draw. Protection for risks are outlined in protection of human subjects.

2.3.2 KNOWN POTENTIAL BENEFITS

The intervention is a noninvasive, minimal risk psychoeducational and cognitive behavioral program that may improve resilience resources and stress responses and ultimately improve better long-term outcomes in people aging with HIV, either directly or indirectly. Thus, the risks associated with this project are minimal, reflecting no more than asking questions and obtaining information that is kept confidential. It is possible that study participants will derive no direct benefit from this research. However, some participants may improve their resilience or other abilities and therefore may also improve their cognitive, physical, or emotional functioning or experience other beneficial symptom outcomes which may yield benefits for autonomy and quality of life. The data gathered from this study can be used to inform future intervention approaches targeting psychological resilience and resilience resources across aging populations, both clinical and non-pathological.

3 STUDY DESIGN

3.1 OVERALL DESIGN

A two group randomized trial with an intervention group and an attention matched control group. The interventions both include four weekly in person group sessions. Both groups complete assessments at baseline, 1 month (after intervention), and 3 months.

3.2 END OF STUDY DEFINITION

Completion of 3 month follow-up assessment.

4 STUDY POPULATION

4.1 INCLUSION CRITERIA

Initial eligibility criteria include: current university HIV clinic patient, age 45+, no neurological or severe psychiatric (e.g., schizophrenia, bipolar disorder, untreated major depression) disorders, recent history (within the past 12 months) of suboptimal HIV management based on either >=50% of visits with detectable viral load or >=50% of scheduled visits as no show without prior cancellation/reschedule. Those who met EMR eligibility completed a phone screen to determine additional eligibility criteria: diagnosis of HIV for greater than 1 year (confirmed via EMR), owning a smart phone with unlimited texting, living in a house or an apartment (not homeless), able to read and write in English, self-report absence of neurological or severe psychiatric disorders that may not have been captured from EMR (e.g., schizophrenia, bipolar disorder, Alzheimer's disease), self-report absence of other medical conditions that can potentially affect mental/thinking abilities, not being blind or deaf, not currently undergoing radiation or chemotherapy, never experienced brain trauma with loss of consciousness > 30 minutes. The phone screener also asked a series of questions for anyone who had a history of depression in their EMR and had lower than 15 cutoff score for the PHQ-9 depression measure from the EMR: "Have you received any counseling or psychotherapy for any mental health conditions in the last 3 months?", "Are you currently taking any medication for depression and has it been consistent for the 3 months?", and "If YES, do you anticipate any upcoming changes with your medication?". These questions were added as a means of excluding individuals who are currently or recently received counseling or psychotherapy and/or expected their prescription to change, as changes in medication and engagement in counseling or psychotherapy can impart unintended influences on the findings of the resilience intervention.

4.2 EXCLUSION CRITERIA

See above

4.3 SCREEN FAILURES

Participants who did not meet the criteria above were not invited for a baseline assessment, and were considered screen failures.

4.4 STRATEGIES FOR RECRUITMENT AND RETENTION

We recruited via our university HIV outpatient clinic by running eligibility queries of EMR data yielding a list of patients meeting basic criteria that consented to be contacted for future studies. Some participants may have learned of the study via word of mouth from other patients/participants. Compensation was provided for all study visits to increase retention.

5 STUDY INTERVENTION

5.1 STUDY INTERVENTION(S) ADMINISTRATION

5.1.1 STUDY INTERVENTION DESCRIPTION

RISE+: Participants in the intervention group came to the lab for four two-hour weekly sessions in small groups of 3-4. The intervention includes psychoeducational videos and individual written activities on topics such as coping strategies, cognitive appraisals, the responsibility model, and social connections, all integrated into the overarching process of resilience. The intervention was facilitated by a trained research assistant but as in the pilot study, they were minimally involved (i.e., only administering the videos and explaining the activities) to keep the private reflective nature of the program that participants liked. Upon completion of the program, participants were given handouts with summaries of the program material.
Attention control: Control participants completed an attention-matched internet stress reduction paradigm, which includes an internet navigation protocol and placebo computer games and activities. As with the intervention group, participants in the control group came to the lab for four two-hour weekly sessions in small groups of 3-4. Facilitator involvement was the same as the intervention group (e.g., the research assistant explained computer activities and games but will otherwise did not interact with participants).

5.1.2 DOSING AND ADMINISTRATION

Control and intervention groups completed four ~one-hour weekly sessions in small groups of 3-4 at our lab (in person). The interventions were facilitated by a trained research assistant but as in the pilot study, they were minimally involved (i.e., only administering the videos and explaining the activities).

5.2 MEASURES TO MINIMIZE BIAS: RANDOMIZATION

We stratified randomization based on race (white or non-white), sex (male or female), and high (≥ 26) or low resiliency (≤25) based on the Connor Davidson Resilience Scale (described below).

5.3 STUDY INTERVENTION COMPLIANCE

Participants were considered compliant if they completed all four weekly one hour sessions. We allowed for participants to complete the four sessions over a span of up to two months, when needed.

5.4 CONCOMITANT THERAPY

N/A

6 STUDY INTERVENTION DISCONTINUATION AND SUBJECT DISCONTINUATION/WITHDRAWAL

6.1 DISCONTINUATION OF STUDY INTERVENTION

If a participant did not show up to the first (or any intervention session) we attempted to contact them three times before considering them lost to follow-up.

6.2 SUBJECT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Subjects are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a subject from the study for the following reasons:

- Significant study intervention non-compliance

Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

6.3 LOST TO FOLLOW-UP

A subject will be considered lost to follow-up if he or she fails to return for 2 scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a subject fails to be available for a required study visit:

- The site will attempt to contact the subject and reschedule the missed visit and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain if the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record or study file.
- Should the subject continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

7 STUDY ASSESSMENTS AND PROCEDURES

7.1 STUDY ASSESSMENTS

The baseline survey consists of the measures below delivered via a REDCAP survey at our lab, plus a 10-day ESM protocol. The one-month posttest includes all baseline measures except the Ten-Item Personality Inventory (TIPI), Alcohol, Smoking and Substance Involvement Screening Test – Lite (ASSIST-Lite), the Childhood Traumatic Events Scale (CTES), and the Recent Traumatic Events Scale (RTES), plus an exit survey and a 10-day ESM protocol. Finally, the three-month follow-up includes the same measures used in the one-month post-test except the exit survey.

***Background Information*:**
Substance Use: Alcohol, Smoking and Substance Involvement Screening Test – Lite (ASSIST-Lite)
Personality Traits: *The Ten-Item Personality Inventory (TIPI)*
Trauma History: The Childhood Traumatic Events Scale (CTES) and the Recent Traumatic Events Scale (RTES)
Stress: The Perceived Stress Scale (PSS)
Anxiety: Generalized Anxiety Disorder 7 item scale (GAD-7)
Depressive Symptoms: The Center for Epidemiologic Studies Depression Scale (CESD)
Resilience: The Connor Davidson Resilience Scale 10 item (CDRS-10)
Coping Skills: The Brief COPE
Locus of Control: Personality in Intellectual Aging Contexts (PIC) Inventory Control Scales Short Form
Social Support: The Duke Social Support Index (DSSI)
HIV Stigma: The HIV Stigma Scale (HSS-32)
Quality of Life/Wellbeing: The Medical Outcome Study (MOS) RAND 36-Item Short-Form Health Survey (RAND 36SF)
HIV Treatment Management: The HIV Treatment Adherence Self-Efficacy Scale (HIV-ASES)
HIV Medication Adherence: The Visual Analogue Scale (VAS)

Exit Survey: Participants in both the RISE+ arm and control arm are administered a 15-item survey to provide feedback on their experiences during the study. The survey consists of both closed and open-ended questions, allowing a full range of responses. Sample items include: “On scale of 1 to 10, with 10 being the highest, overall, how would you rate this intervention?” and “What did you like or find helpful about this program? In other words, what should we leave as is?”

ESM Protocol. Prior to the first ESM assessment, we conduct a 15-minute training at baseline. We use a validated ESM protocol which includes twice a day text messages (morning and evening) for 10 days following both baseline and one month post intervention. Automated text messages based on morning and evening times selected by participants are sent to participants’ personal phones that contain a web link to complete the Redcap survey. If a participant does not report a stressor for item 1, they select “NA” for resilience resource items. The survey takes ~three minutes. If a participant does not respond to a survey, a reminder message is sent one hour later. If a participant has not responded to any survey for 24 hours, we contact them to troubleshoot and encourage reporting.

7.2 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

7.2.1 DEFINITION OF ADVERSE EVENTS (AE)

The intervention involves minimal risk. It is a behavioral resilience building intervention, and includes testing the efficacy of this intervention on psychosocial functioning and HIV outcomes.

No adverse events (AEs), serious adverse events (SAEs), or unanticipated problems (UPs) are expected as a result of the proposed intervention or data collection methods. However, if any such events should occur, even if they are not believed to be related to the intervention, the study staff will report these events to the PI, who will report these events to the safety officer (SO), IRB, and NIA.

AEs, SAEs, and UPs, will be defined as follows:

AE: Any untoward or unfavorable medical occurrence in a human study participant, including any abnormal sign (e.g. abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participants' involvement in the research, whether or not considered related to participation in the research.

7.2.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Results in death
- Is life threatening, or places the participant at immediate risk of death from the event as it occurred
- Requires or prolongs hospitalization
- Causes persistent or significant disability or incapacity
- Results in congenital anomalies or birth defects
- Is another condition which investigators judge to represent significant hazards

7.2.3 CLASSIFICATION OF AN ADVERSE EVENT

7.2.3.1 SEVERITY OF EVENT

AEs will be reviewed, assessed, and monitored and documented according to classifications of severity, expectedness, and potential relatedness to the study intervention. These classifications include:

Severity Classifications:

- Mild: Awareness of signs or symptoms, but easily tolerated and are of minor irritant type causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient.
- Moderate: Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities, but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning
- Severe: Events interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating

7.2.3.2 RELATIONSHIP TO STUDY INTERVENTION

The potential event relationship to the study intervention and/or participation will be assessed by the PI. A comprehensive scale in common use to categorize an event is:

- Definitely Related: The adverse event is clearly related to the investigational agent/procedure – i.e. an event that follows a reasonable temporal sequence from administration of the study intervention, follows a known or expected response pattern to the suspected intervention, that is confirmed by improvement on stopping and reappearance of the event on repeated exposure and that could not be reasonably explained by the known characteristics of the subject's clinical state.
- Possibly Related: An adverse event that follows a reasonable temporal sequence from administration of the study intervention follows a known or expected response pattern to the suspected intervention, but that could readily have been produced by a number of other factors.

- Not Related: The adverse event is clearly not related to the investigational agent/procedure - i.e. another cause of the event is most plausible; and/or a clinically plausible temporal sequence is inconsistent with the onset of the event and the study intervention and/or a causal relationship is considered biologically implausible.

7.2.3.3 EXPECTEDNESS

AEs will be assessed as to whether they were expected to occur or unexpected, meaning not anticipated based on current knowledge found in the protocol, investigator brochure, product insert, or label. Categories are:

- Unexpected - nature or severity of the event is not consistent with information about the condition under study or intervention in the protocol, consent form, product brochure, or investigator brochure.
- Expected - event is known to be associated with the intervention or condition under study

7.2.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study subject presenting for medical care, or upon review by a study monitor.

All AEs including will be documented. Information to be collected, when applicable, includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an AE. However, if the study subject's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

7.2.5 ADVERSE AND SERIOUS ADVERSE EVENT REPORTING

The NIA AE/SAE process flow chart will be used by all study staff. If any AEs SAEs, or UPs occur, the appropriate NIA form will be filled out and routed to the appropriate entity in the timeline suggested on the process flow chart. Importantly, any AEs, SAEs or UPs whether or not they are related to the study will be reported to the SO, IRB, and NIA within 48 hours of our knowledge of the event (except for deaths which will be reported within 24 hours regardless of study relatedness). Specifically:

- All **adverse events that are both serious** (SAE) **and unexpected** (i.e., have not been previously reported for the study's intervention), will be reported to IRB, NIA PO and to the SO, **within 48 hours** of the study's knowledge of SAE.
- The summary of all other SAEs will be reported to NIA Program Officer (PO) and to the SO **quarterly**, unless otherwise requested by the SO.
- All deaths will be reported **within 24 hours** of study's knowledge. The report of death will be submitted to NIA PO and to the SO.
- AEs will be reported per IRB policies. They will also be reported the NIA PO and the study's SO, at frequency requested by NIA and/or by the SO. At minimum, annual reports are required.

7.3 UNANTICIPATED PROBLEMS

7.3.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

UP: 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 study population;
• related or possibly related to participation in the research (in this 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);
• suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.3.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

8 STATISTICAL CONSIDERATIONS

8.1 STATISTICAL HYPOTHESES

- Primary Efficacy Endpoint(s):

Changes in resilience resource use, stress reactivity and recovery at one month

- Secondary Efficacy Endpoint(s):

Changes in health outcomes (i.e., psychological functioning [quality of life, depressive symptomatology], and HIV outcomes [ART and visit adherence, treatment self-efficacy, viral suppression, and CD4 count]) at 1 and 3 months after the end of the intervention.

8.2 SAMPLE SIZE DETERMINATION

We considered: A) a repeated-measures design for Specific Aim 1a (change in use of resilience resources measured by ESM between the baseline and post intervention ESM periods); B) 80% power, $(1 - \beta = .8)$ to detect a time-averaged mean difference in change in resource use if it exists between the intervention group and the placebo groups; C) an average of 10 stress events per individual per period; D) a significance level adjusted for a False Discovery Rate (10% FDR) assuming relevant intervention effects on at least 30% the outcomes, $\alpha = .1$ X 2/7 = .028; and E) intra-subject correlation of $\rho = .5$ among repeated measurements on the same participants. With an effective sample size of N=80 (after 20% attrition) the detectable difference is d=.22, a small effect.

8.3 STATISTICAL ANALYSES

8.3.1 GENERAL APPROACH

See below

8.3.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

Specific Aim 1 examines the effects of the intervention on **ESM outcomes** (multilevel data collected twice a day for 10 days at baseline and 1 month): a) resilience resource use; and b) stress reactivity. For each resource outcome, the intervention effect was estimated as the mean between-group difference in change from baseline to post-intervention periods. We also examined intervention effects on **traditional measures** (only assessed at baseline, 1 month, 3 months) of resilience and stress.

Conditional mixed models with baseline adjustment were fitted to these outcomes, including random effects for subject and day (within-subject) to account for the multilevel structure of the data, fixed effects for group assignment, time period, and interaction between group assignment and period to participants using all available data.

Conditional generalized mixed model was used for stress reactivity. Stress reactivity is operationalized as the difference in affect between a stressor instance and proximally *preceding* non-stressor instance, and recovery is the difference in affect between a stressor instance and a proximally *subsequent* non-stressor instance. We processed the within-person data stream by ESM period to identify dyads of ESM instances with the patterns non-stressor → stressor (for reactivity) and stressor → non-stressor (for recovery).

Separately for reactivity and recovery, a 'constrained' longitudinal model was used also with baseline adjustment (conditioning). A two-way interaction between group and period was used to estimate between-group differences in change on reactivity/recovery from baseline to post-intervention.

When examining traditional resilience measure outcomes (only assessed at baseline, 1 month, 3 months), for each outcome, a linear mixed model with random effects for subject and time was fitted with a group assignment indicator, time-point indicator (baseline, one month, three month), and group by time-point interaction as fixed effects. The intervention effect was estimated by the interaction term. Confidence intervals were computed to assess uncertainty of all effect estimates.

8.3.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Specific Aim 2 examines intervention effects on psychological functioning and HIV outcomes. For each outcome, a linear mixed model with random effects for subject and time was fitted with a group assignment indicator, time-point indicator (baseline, one month, three month), and group by time-point interaction as fixed effects. The intervention effect was estimated by the interaction term. Confidence intervals were computed to assess uncertainty of all effect estimates.

8.3.4 SAFETY ANALYSES

N/A

8.3.5 BASELINE DESCRIPTIVE STATISTICS

Baseline characteristics were tabulated, and measures of effect size (Cramer's V and Cohen's d) were used to examine whether relevant chance imbalances between groups were present.

9 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

9.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

9.1.1 INFORMED CONSENT PROCESS

9.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO SUBJECTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the subject and written documentation of informed consent is required prior to conducting study screening procedures. A separate screening consent form will not be used.

9.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

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. Consent forms will be Institutional Review Board (IRB)-approved and the subject will be asked to read and review the document. The investigator will explain the research study to the subject and answer any questions that may arise. A verbal explanation will be provided in terms suited to the subject's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research subjects. Subjects will have the opportunity to carefully review the written consent form and ask questions prior to signing. The subjects should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The subject will sign the informed consent document prior to any procedures being done specifically for the study. Subjects must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the

informed consent document will be given to the subjects for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the subject undergoes any study-specific procedures. The rights and welfare of the subjects 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.

9.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study subjects and the Institutional Review Board (IRB), will provide the reason(s) for the termination or suspension. Study subjects will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the IRB.

9.1.3 CONFIDENTIALITY AND PRIVACY

Subject confidentiality and privacy is strictly held in trust by the participating investigators and their staff. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Principal Investigator.

All research activities will be conducted in as private a setting as possible.

Representatives of the Institutional Review Board (IRB) may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

The study subject's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB and/or Institutional policies.

Study subject research data, which is for purposes of statistical analysis and scientific reporting, will be stored at the UAB Department of Otolaryngology research office. This will not include the subject's contact or identifying information. Rather, individual subjects and their research data will be identified by a unique study identification number. The study data entry and study management systems used by research staff will be secured and password protected.

9.1.4 QUALITY ASSURANCE AND QUALITY CONTROL

The site will perform internal quality management of study conduct, data collection, documentation and completion. Quality control (QC) procedures will be completed by the Data Manager during data entry into the appropriate CRF. Any missing data or data anomalies will be communicated to the Study Coordinator for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements.

The site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and inspection by local and regulatory authorities.

9.1.5 DATA HANDLING AND RECORD KEEPING

9.1.5.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the Principal Investigator. The Principal Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hard copies of source document worksheets will be used for recording data for each subject enrolled in the study. Data recorded in the case report form (CRF) derived from source documents should be consistent with the data recorded on the source documents.

9.1.5.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 3 years after the completion of the study. These documents should be retained for a longer period, however, if required by local regulations.

9.1.6 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol requirements. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the Principal Investigator to use continuous vigilance to identify and report deviations within 10 working days of identification of the protocol deviation. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The Principal Investigator is responsible for knowing and adhering to the reviewing IRB requirements.

9.1.7 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

9.2 ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DHHS	Department of Health and Human Services
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional Review Board
LSMEANS	Least-squares Means
NCT	National Clinical Trial
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOA	Schedule of Activities
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10 REFERENCES