Telehealth High Intensity Interval Exercise and Cardiometabolic Health in Spinal Cord Injury

Study Protocol & Statistical Analysis Plan

NCT #04940598

July 13, 2023

Gordon Fisher, Ph.D. Principal Investigator
University of Alabama at Birmingham
Birmingham, AL 35294

Telehealth High Intensity Interval Exercise and Cardiometabolic Health in Spinal Cord Injury

Principal Investigator: Gordon Fisher

Sponsor: University of Alabama at Birmingham

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	**Telehealth high intensity interval exercise and cardiometabolic health in spinal cord injury**
Study Description:	This study will determine if the implementation of a home-based telehealth high intensity interval exercise-training (HIIT)program can significantly improve cardiometabolic health and physical function in a cohort of individuals with longstanding spinal cord injury (SCI). Results from this study will determine feasibility, overall enjoyment, and health impact of implementing a home-based telehealth HIIT program in individuals with SCI.
Objectives:	The goal of this study is to integrate a home-based telehealth HIIT arm crank exercise training program in individuals with SCI and assess changes in cardiometabolic health and physical function. The secondary goal is to explore the uptake and implementation of HIIT in SCI.
Study Population:	1. Individuals 19-65 years old with confirmed diagnosis of traumatic SCI at the cervical or thoracic level (C7-T12), classified as A, B, C, or D (motor and sensory complete or incomplete) on the AIS scale. 2. At least 6 months post-injury.
Phase:	Not Applicable

Description of Study Intervention:	•
	  ○ HIIT training will be delivered two times per week for 16 weeks (32 sessions). Each session will be separated by at least 24-hrs. Participants will be allowed to choose the days and times that they feel exercise will fit into their schedule. The HIIT protocol will be determined based on peak anaerobic power measures during an arm crank Wingate Cycle test. HIIT will consist of 20 minutes of exercise consisting of four minutes of arm crank exercise at 5% of peak anaerobic power followed by 30 seconds at 30% of the peak anaerobic power; this cycle will be repeated four times, ending with two minutes of recovery at 5% of peak anaerobic power.
	• Other: No-exercise control group
	  ○ No-exercise control group

Study Duration:	3 years
Subject Duration:	6 months

INTRODUCTION

1.2 STUDY RATIONALE

For individuals with spinal cord injury (SCI), exercise participation reduces the risk of developing chronic cardiometabolic diseases, which are leading causes of rehospitalization and death within this population. Accordingly, recent SCI exercise guidelines have highlighted a need for exercise trials that can improve cardiometabolic factors such as glucose tolerance, blood lipids, blood pressure, and body composition. However, to date, the number of exercise trials examining these cardiometabolic outcomes in SCI is low, and these exercise regimens are often inconvenient for individuals with SCI to perform within their community. In addition to the functional impairment associated with the disability, individuals with SCI experience a number of barriers to exercise participation, such as lack of time (e.g. conflict with work schedule), accessible or usable equipment and facilities, and transportation. Thus, it is important to identify effective modes of exercise that can improve overall health but do not require a significant overall weekly time commitment. Investigators recently demonstrated that individuals with SCI could safely perform high intensity interval training (HIIT) using arm crank cycling and that as few as two days per week of HIIT could improve cardiometabolic health. Despite the advantages of HIIT, it is important to identify methods of implementing exercise trials that can successfully reach and maintain participation in larger cohorts. Recent work by the investigative group demonstrated that individuals with SCI expressed favorable perceptions of home-exercise training that incorporated telehealth technology, which allowed a fitness specialist to remotely monitor participants' training progress in real-time and provide verbal support via videoconferencing. This method of training holds even greater value for home-exercise programs that require monitoring to dose-specific protocols such as HIIT. However, the long-term success of HIIT will greatly depend on the ease at which the program can be implemented, as well as participants' adherence and perceptions of using the technology, which has not been investigated in SCI. The goal of this study is to integrate a home-based telehealth HIIT arm crank exercise training program in individuals with SCI and assess changes in cardiometabolic health and physical function. The secondary goal is to explore the uptake and implementation of HIIT in SCI. 40 participants will be randomized to home-based HIIT exercise or a no-exercise control group for 16-weeks. Body composition, aerobic fitness, muscular strength, and changes in cardiometabolic health will be assessed at baseline and 16-weeks post training. In addition to changes in cardiometabolic health outcomes, the investigators will also conduct interviews with participants to determine overall perceptions of the program, program likes and dislikes, perceived satisfaction and value, usability of equipment and technology, and factors that influence adherence.

2 STUDY DESIGN

2.1 OVERALL DESIGN

Primary Purpose : Prevention
Allocation : Randomized
Interventional Model : Parallel Assignment
Interventional Model Description: In a longitudinal study design, 40 participants with chronic SCI will be randomly assigned to one of the two study groups (HIIT and control) in a 1:1 ratio. Randomization will be performed using the block randomization method, Randomization will be performed using the block randomization method. A randomization list will be generated and assignments will be placed into

closed envelopes and given to each study participant. Participants will be assessed at baseline and 16-wks post HIIT or control

3 STUDY POPULATION

3.1 INCLUSION CRITERIA

1. Men and women, 19-65 years of age.
2. Confirmed diagnosis of traumatic SCI at the cervical or thoracic level (C7-T12), classified as A, B, C, or D (motor and sensory complete or incomplete) on the AIS scale.
3. At least 3 years post-injury.
4. Able to independently operate an arm ergometer.
5. Have access to a wireless internet connection.
6. Medically stable, able to provide informed consent

3.2 EXCLUSION CRITERIA

1. Cardiovascular or renal diseases.
2. Pregnant women
3. Orthopedic conditions that prevents arm ergomtery
4. Upper extremity musculoskeletal conditions that prevents arm ergometry.
5. Neurological disorder that prevents arm ergometry
6. Participation in a structured exercise program currently or in the past 3 months.
7. Unable to perform exercise interventions

4 STUDY INTERVENTION

4.1 STUDY INTERVENTION(S) ADMINISTRATION

4.1.1 STUDY INTERVENTION DESCRIPTION

In a longitudinal study design, 40 participants with chronic SCI will be randomly assigned to one of the two study groups (HIIT and control) in a 1:1 ratio. Randomization will be performed using the block randomization method, Randomization will be performed using the block randomization method. A randomization list will be generated and assignments will be placed into closed envelopes and given to each study participant. Participants will be assessed at baseline and 16-wks post HIIT or control Home-Based Telehealth Exercise Intervention will include implementation of HIIT training performed on an arm crank cycle ergometer. The teleexercise will be delivered through a custom, wireless Internet-based system that will be installed in the participant's home. The equipment within this system includes a tablet computer (Samsung Galaxy Tab 2 10.1, Samsung) with Bluetooth® and wireless Internet capability mounted to an adjustable floor stand (Standzfree Universal Stand, Standzout); wearable physiologic monitor (Bioharness 3, Zephyr) that provides real-time monitoring of heart and respiration rate data to the tablet via Bluetooth® connection; and custom-designed web application that allows physiologic data and video feed to be recorded from the tablet to a secure web-based dedicated server.

This platform allows the exercise trainer (telecoach) to monitor each participant's physiologic data in real-time (up to 5 second delay) while simultaneously video-conferencing and providing written instructions to the participant.. Telecoaches will utilize this system to provide immediate feedback regarding exercise intensity and movement quality during each exercise session. All exercise sessions will be performed on an upper body ergometer (UBE-BDP Table Top Upperbody Exerciser, Hudson Fitness). HIIT training will be delivered two times per week for 16 weeks (32 sessions). Each session will be separated by at least 24-hrs. Participants will be allowed to choose the days and times that they feel exercise will fit into their schedule. The HIIT protocol will be determined based on peak anaerobic power measures during an arm crank Wingate Cycle test. HIIT will consist of 20 minutes of exercise consisting of four minutes of arm crank exercise at 5% of peak anaerobic power followed by 30 seconds at 30% of the peak anaerobic power; this cycle will be repeated four times, ending with two minutes of recovery at 5% of peak anaerobic power. The use of percent workload is important as use of heart rate to prescribe exercise is not accurate in many individuals with SCI, as the sympathetic nervous system input is often impaired. Based on our preliminary data in which some participants had difficulty performing intervals using 50% of peak anaerobic power, this protocol will utilize a more modest 30% of peak anaerobic power exercise, which should be more feasible and achievable for all participants. This workload will still be higher than corresponding VO2 peak workloads, thus will still elicit a high intensity interval session. The participants will be coached and monitored remotely via the telehealth system. Heart rate and respiratory rate will be monitored throughout each session.

4.2 MEASURES TO MINIMIZE BIAS: RANDOMIZATION

Randomization will be performed using the block randomization method, Randomization will be performed using the block randomization method. A randomization list will be generated and assignments will be placed into closed envelopes and given to each study participant.

5 STUDY INTERVENTION DISCONTINUATION AND SUBJECT DISCONTINUATION/WITHDRAWAL

5.1 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
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject

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.

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.

6 STUDY ASSESSMENTS AND PROCEDURES

6.1 STUDY ASSESSMENTS

Body Composition, Resting Energy Expenditure, Insulin Sensitivity, Blood Pressure, blood lipids, Aerobic Capacity, Anaerobic Capacity.

6.2 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

6.2.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

6.2.2 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:

- Death
- A life-threatening adverse event (of note, the term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event, rather than to an event which hypothetically might have caused death if it were more severe)
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- or a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

6.2.2.1 SEVERITY OF EVENT

For adverse events (AEs), the following guidelines will be used to describe severity:

- **Mild** – Events require minimal or no treatment and do not interfere with the subject's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a subject's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious."

6.2.2.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the subject based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

6.2.2.3 EXPECTEDNESS

The Principal Investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

6.2.3 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 local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected 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.

The Study Coordinator will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the Study Coordinator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

6.2.4 ADVERSE AND SERIOUS ADVERSE EVENT REPORTING

All serious adverse events must be reported to the IRB according to regulatory requirements. The Principal Investigator will immediately report to the sponsor any serious adverse event, whether or not

considered study intervention related, including those listed in the protocol or package insert and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the Principal Investigator deems the event to be chronic or the subject is stable. Other supporting documentation of the event may be requested and should be provided as soon as possible.

6.3 UNANTICIPATED PROBLEMS

6.3.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

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 Institutional Review Board (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 ("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.

6.3.2 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.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB within 10 working days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB within 10 working days of the investigator becoming aware of the problem.

7 STATISTICAL CONSIDERATIONS

7.1 STATISTICAL HYPOTHESES

- Primary Efficacy Endpoint(s):
- Change in Aerobic Capacity [Time Frame: baseline]
    - All subjects will undergo a progressive peak oxygen assessment to determine aerobic capacity at the Lakeshore Foundation Exercise Physiology Facility. Subjects will be instructed to perform arm crank ergometer (Lode) at 10W for 2 min. Every 2 min thereafter, power output will be increased by 10W until voluntary fatigue. Peak aerobic power will be defined as VO2 at the point of failure to maintain 60-65 rotations per minute.
- Change in Aerobic Capacity [Time Frame: 16weeks post training]
    - All subjects will undergo a progressive peak oxygen assessment to determine aerobic capacity at the Lakeshore Foundation Exercise Physiology Facility. Subjects will be instructed to perform arm crank ergometer (Lode) at 10W for 2 min. Every 2 min thereafter, power output will be increased by 10W until voluntary fatigue. Peak aerobic power will be defined as VO2 at the point of failure to maintain 60-65 rotations per minute.
- Change in Muscular Strength [Time Frame: baseline]
    - Muscle Strength Assessment. Maximal load that can be lifted in one repetition (1RM) will be assessed in both limbs for chest press, elbow flexion, and shoulder flexion maneuvers.
- Change in Muscular Strength [Time Frame: 16weeks post]
    - Muscle Strength Assessment. Maximal load that can be lifted in one repetition (1RM) will be assessed in both limbs for chest press, elbow flexion, and shoulder flexion maneuvers.
- Change in Insulin Sensitivity [Time Frame: baseline]
    - Oral glucose tolerance test. Following an overnight fast each subject will consume a 75g oral glucose load within 5 min. Blood samples will be collected immediately before and 60, 90, and 120 min following glucose ingestion for measurement of serum glucose and serum insulin.
- Change in Insulin Sensitivity [Time Frame: 16weeks post training]
    - Oral glucose tolerance test. Following an overnight fast each subject will consume a 75g oral glucose load within 5 min. Blood samples will be collected immediately before and 60, 90, and 120 min following glucose ingestion for measurement of serum glucose and serum insulin.
- Change in Blood Lipids [Time Frame: baseline]
    - Laboratory analyses. Concentrations of blood lipids will be determined in the Core Laboratory of the CCTS, NORC, and DRC.
- Change in Blood Lipids [Time Frame: 16weeks post training]
    - Laboratory analyses. Concentrations of blood lipids will be determined in the Core Laboratory of the CCTS, NORC, and DRC.
- Change in Body Composition [Time Frame: baseline]

    - Dual-energy X-ray absorptiometry (DXA). Total and regional body composition will be measured by DXA (Lunar Radiation Corp., Madison, WI) at the Lakeshore Foundation Research Facility.
- Change in Body Composition [Time Frame: 16weeks post training]
    - Dual-energy X-ray absorptiometry (DXA). Total and regional body composition will be measured by DXA (Lunar Radiation Corp., Madison, WI) at the Lakeshore Foundation Research Facility.
- Change in Blood Pressure [Time Frame: baseline]
    - Systolic and Diastolic blood pressure will be assessed using standard blood pressure cuff and a stethoscope.
- Change in Blood Pressure [Time Frame: 16weeks post training]
    - Systolic and Diastolic blood pressure will be assessed using standard blood pressure cuff and a stethoscope.

- Secondary Efficacy Endpoint(s):

Semi-Structured Interview [Time Frame: 16 weeks post-training]
The semi-structured interviews will contain seven open-ended questions related to the following areas: 1) overall perceptions of the program, 2) program likes, 3) dislikes, 4) perceived satisfaction and 5) value, 6) technology and equipment usability, and 7) factors that affected adherence. These areas will be probed in greater detail by the interviewer through additional follow-up questions.

7.2 SAMPLE SIZE DETERMINATION

40 participants will be randomized to home-based HIIT exercise or a no-exercise control group for 16-weeks.

7.3 STATISTICAL ANALYSES

Descriptive statistics, such as means, standard deviations, and 95% confidence intervals, will be calculated for all study variables of interest. The primary method of analysis will be mixed models repeated measures analyses, such as repeated measures analysis of covariance. This will allow us to test the group, time, and group by time interaction effect simultaneously. An appropriate structure for the covariance matrix (e.g. the unstructured covariance matrix) will be selected for these models using the final data. The Tukey-Kramer multiple comparisons test will be used as the *post hoc* test of choice for these analyses. ***Biological variables, such as age, sex, race, and %fat, will be accounted for in these models (see Rigor and Reproducibility in Statistical Design and Power document for details)*** Overall comparisons between means of the two groups will be performed using the two-group t-test, and overall changes within groups will be examined using the paired t-test. Correlation analysis will be performed, with Pearson correlation coefficients being calculated for pairs of continuous variables. Distributions of continuous variables will be examined for normality using box plots, stem-and-leaf plots, and normal probability plots; those deviating greatly from a normal distribution will be log transformed or analyzed using appropriate nonparametric tests such as the Wilcoxon rank-sum and signed-rank tests. Multiple imputation methods may be used to address missing data for variables with moderate amounts of missing data (≥10%) and after examining whether data are missing completely at random (MCAR), at

random (MAR), or not at random (MNAR). Statistical tests will be two-sided and will be performed using a 5% significance level. SAS software, version 9.4 or later, will be used to conduct the statistical analyses.

8 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

8.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

8.1.1 INFORMED CONSENT PROCESS

- We will consent all participants in a private room with study personnel.

8.1.1.1 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.

8.1.1.2 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.

8.1.2 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.

8.1.3 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.

8.1.4 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.

8.1.5 DATA HANDLING AND RECORD KEEPING

All research data will be stored on password-protected computer systems housed in the Department of Human Studies and/or the Department of Nutrition Sciences (glucose tolerance data and blood lipids). Confidentiality will be maintained as each participant will be assigned a code which will then be the identifier within data files containing dependent variables. Files linking the participant name to participant code will be will be stored electronically in a folder and access will be limited to the PI (Fisher). Hard copies of participant records (e.g. consent form, and form W-9) will be maintained in a locked file cabinet. Only the PI will have access to the locked file cabinet.

8.1.5.1 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.

8.1.5.2 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.

8.1.6 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.

8.1.7 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.

8.2 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