Evaluating the Implementation and Impact of Navigator-delivered ePRO System

Study Protocol & Statistical Analysis Plan

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Evaluating the Implementation and Impact of Navigator-delivered ePRO System

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Sponsor: National Institute of Nursing Research

National Clinical Trial (NCT) Identified Number: <NCT number>

Version Number: v1.0

05/27/2025

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:	Evaluating the Implementation and Impact of Navigator-delivered ePRO System
Study Description:	Randomized controlled trials demonstrated that weekly electronic home-based PRO symptom monitoring with automated alerts to clinicians (Home ePRO) in cancer patients was associated with reduced healthcare utilization, improved quality of life, and increased overall survival. However, these trials were administered using infrastructure supported by research funding. A knowledge gap remains about optimal implementation strategies for and effectiveness of Home ePROs in real-world settings. To address this gap, we will conduct a large-scale population-based implementation of an evidence-based Home ePRO intervention for all adult cancer patients receiving chemotherapy. The investigators' hypothesis is that the deployed implementation strategies will result in successful navigator-delivered Home ePRO, which will improve both patient and health system outcomes.
Objectives:	Evaluate implementation of navigator-delivered Home ePRO for all cancer patients and assess the impact of Home ePRO on clinical and utilization outcomes.
Endpoints:	Primary Outcome Measure: 1. Service Penetration [Time Frame: up to 3 months of starting a treatment for cancer] % of eligible patients enrolled Secondary Outcome Measures: 1. Proportion of Alerts Closed Within 48 Hours [Time Frame: up to 48 hours]

	alerts are measured by abstracting alert data from the ePRO database 2. % of Patients Completing ≥1 ePRO Survey [Time Frame: up to 6 months] ePRO surveys are abstracted from the electronic patient-reported outcome system 3. % of Expected ePRO Surveys Completed Per Patient [Time Frame: up to 6 months] ePRO surveys are abstracter from the database; the surveys completed are compared to those sent 4. % of Surveys Completed of Surveys Sent to Patient [Time Frame: up to 6 months] ePRO surveys are abstracted from the ePRO database including surveys completed 5. Symptom Trajectory [Time Frame: up to 3 months; up to 6 months] abstract from ePRO database the symptom alerts; we will report the proportion alerting for the population over 6 months 6. Number of ED Visits [Time Frame: up to 3 months, up to 6 months] Proportion with patients with an ED visit (abstracted from the electronic medical record) 7. Number of Hospitalizations [Time Frame: up to 3 months, up to 6 months] Proportion of patients hospitalized (abstracted from the EMR) 8. Number of ICU Visits [Time Frame: up to 3 months, up to 6 months] Proportion admitted to the ICU 9. Total Cost of Care [Time Frame: up to 3 months, up to 6 months] total costs sent by UAB to payers (abstracted from billing records)
Study Population:	Adults with cancer receiving chemotherapy, targeted therapy, and immunotherapy at participating institution from 2019-2025.
Phase:	N/A
Description of Study Intervention:	Enrollment in program that includes standard of care weekly symptom survey delivery to patients, with alerts generated for symptoms that are sent to clinic nurses to address per standard of care protocol
Study Duration:	5/4/2021 – 2/28/2027
Subject Duration:	6 months

2 INTRODUCTION

2.1 STUDY RATIONALE

Proactive symptom management using electronic patient-reported outcomes (ePROs) is associated with improved patient satisfaction and symptom control. Randomized trials demonstrated that weekly symptom monitoring using home-based ePROs was associated with reduced emergency department and hospital visits, longer treatment duration, improved quality of life, and increased survival for patients with advanced cancer. However, these randomized trials were conducted with personnel and infrastructure supported by research funding. Thus, the intervention has not been widely implemented. A knowledge gap remains about optimal implementation and effectiveness of ePROs for symptom monitoring and management (Home ePRO), a multi-level intervention, in real- world settings.

The University of Alabama at Birmingham and the University of South Alabama (MCI) are implementing Home ePRO using existing health system infrastructure for all cancer patients receiving chemotherapy as standard of care using patient navigators, a natural workforce for HOME ePRO. This provides a unique opportunity to study implementation.

2.2 BACKGROUND

Patients benefit from routine collection of electronic patient-reported outcomes (ePROs) to monitor and proactively manage symptoms. Previous studies have reported associations between routine collection of ePROs and 1) improved efficiency of symptom assessment; 2) patient-clinician communication and satisfaction; and 3) symptom control and well-being. In patients with advanced cancer, a randomized trial by Basch and colleagues demonstrated that between visits, weekly electronic home-based PRO symptom monitoring with automated alerts to clinicians (Home ePRO) was associated with reduced emergency department (ED) and hospital visits, improved health-related quality of life, and a 5-month increase in overall survival. This survival advantage was corroborated by a multisite randomized trial in advanced lung cancer patients, which found a 7-month median survival benefit for Home ePRO. Notably, the survival benefits observed in these studies are greater than the benefits reported by many therapeutic interventions approved by the Food and Drug Administration in the past 5 years. Both studies were randomized trials for testing efficacy.

Few general oncology practices utilize Home ePROs due to lack of real-world data on implementation. Although 80-85% of patients in studies were willing and able to self-report symptoms in ePRO trials, *research funding* supported Home ePRO administration. Studies did not enroll patients at the population level, where implementation is limited by the personnel and infrastructure capacity of the healthcare system. Furthermore, only 9% of study participants were African American, and few lived in

rural areas. Limited data is available on the use of Home ePRO in vulnerable populations. Thus, there remains a *substantial knowledge gap* about optimal strategies for Home ePRO implementation in real-world settings where all patients in a cancer center participate, including diverse populations that may differ in participation rates and outcomes.

Leveraging the changing data landscape created by value-based healthcare. The transition toward value-based healthcare has generated substantial opportunities for innovation in healthcare delivery. In 2016, the Centers for Medicare and Medicaid Innovation launched a nationwide payment reform demonstration project, the Oncology Care Model (OCM). Participating practices receive administrative claims data to improve care through data review and analysis. Thus, practices gain experience in merging local clinical data with claims data for the purposes of pragmatically evaluating programmatic success. Early data suggest positive results. Medicare's data sharing resulted in other payers sharing data with institutions who provide care for their beneficiaries. Such data will be used for the proposed research.

The OCM and the proposed Oncology Care First Model (Medicare's proposed payment reform project) require use of navigators for care coordination, providing a natural workforce for effective implementation of Home ePRO. Our 2012 Center for Medicare and Medicaid Innovation project showed increased value from implementation of patient navigation services across the southeastern U.S. Based in part on this seminal work, the OCM requires patient navigation in all >100 participating practices across the US. Participating sites utilize additional funding provided by OCM to support their navigation programs. The goals of navigation include enhancing care coordination and proactively managing patient concerns. Patient navigation programs have proven efficacious for increasing access to care, care coordination, symptom management, and reducing cost. These demonstrated benefits contribute to the growing number of nurse and lay (non-clinical) navigation programs, particularly for practices in underserved communities. The University of Alabama at Birmingham (UAB) and the University of South Alabama Mitchell Cancer Institute (MCI) have substantial experience with navigator-led supportive care interventions and navigator-led collection of patient-reported functional status, depression, and distress. Importantly, our navigation programs emphasize support for vulnerable populations, including racial/ethnic minorities (25%), rural residents (30%), and socioeconomically disadvantaged people (10% eligible for Medicare and Medicaid). The patient navigation workforce is ideally positioned to assume a leadership role in Home ePRO implementation, as collecting and responding to PROs aligns with their natural roles and responsibilities.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Participants will not receive any treatment as part of this study, minimizing physical risks. This project will make use of health and other personal information about the study participants. The primary risk to the participants will be loss of confidentiality leading to potential psychological, financial, or legal consequences. We believe that the likelihood of confidentiality breach is very low. For patient participants their choice to participate will not impact their care in any way.

2.3.2 KNOWN POTENTIAL BENEFITS

Study participants may benefit by receiving additional information about improving symptom screening and management. Our findings could benefit future cancer patients by identifying implementation strategies which enhance likelihood of proactive symptom screening and management. This intervention, with proactive management from clinical staff has been shown in prior randomized clinical trials to benefit symptom management and quality of life.

3 STUDY DESIGN

3.1 OVERALL DESIGN

This is a hybrid design implementation trial. The intervention is delivered as standard of care. We will use secondary data to evaluate both process outcomes and patient outcomes associated with implementation of remote symptom monitoring (Home ePRO).

4 STUDY POPULATION

4.1 INCLUSION CRITERIA

Patient Group:

- Age ≥18
- Cancer patients at participating institution
- Receipt of chemotherapy, targeted therapy, and immunotherapy at participating institution from 2019-2026.

4.2 EXCLUSION CRITERIA

Exclusion Criteria: Second opinion only at participating institution.

4.3 STRATEGIES FOR RECRUITMENT AND RETENTION

Patients are observed; all engagement with patients in the intervention is as standard of care

5 STUDY INTERVENTION

5.1 STUDY INTERVENTION(S) ADMINISTRATION

5.1.1 STUDY INTERVENTION DESCRIPTION

Home ePRO: The intervention includes standard-of-care weekly symptom surveys delivered to patients, with alerts for symptoms sent to clinical teams to address per standard-of-care protocols.

5.2 STUDY INTERVENTION COMPLIANCE

Measures of compliance with the intervention were included as process measures in the analysis. There is no direct intervention from the research team with patients.

6 STUDY INTERVENTION DISCONTINUATION AND SUBJECT DISCONTINUATION/WITHDRAWAL

6.1 SUBJECT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

There is a waiver of informed consent for the use of secondary data, as the intervention is delivered as part of standard of care. Patients may withdraw at any time from the intervention through their clinical team.

7 STUDY ASSESSMENTS AND PROCEDURES

7.1 STUDY ASSESSMENTS

Process Outcomes: This component consists of secondary data analysis

Patient Data: Patients will be identified from EMR using ICD-9/10 diagnosis codes for cancer. Data on all patients with cancer seen at participating centers will be abstracted from the EMR. Chart abstraction variables are attached. Data will be abstracted from the EMR using i2b2 (Informatics for Integrating Biology and the Bedside), Carevive (integrated into EMR), UAB Data Warehouse, and OnCore.

Patient Process Outcomes: This will be evaluated using the following outcomes: percentage of patients approached and percentage of patient enrolled of all new patients initiating treatment; percentage completing at least one Home ePRO assessment (evaluation of common symptoms); and percentage completing assessments at 3 and 6 months. Patients are approached by Navigators, who are non-clinical staff whose role is to assist cancer patients and resolve barriers that patients' encounter during their cancer journey.

Provider Data (EHR): Provider data will also be identified through EMR based on their engagement with patients. Data will be abstracted from the EMR using i2b2 (Informatics for Integrating Biology and the Bedside), Carevive, and UAB Data Warehouse. This data will include the provider who received alerts, closed alerts, time to close the alert, and action selected when addressing the symptom.
All outcomes will be abstracted from databases and analyzed using SAS or R.

Patient Outcomes: We will evaluate the impact of Home ePROs: on the following outcomes: patient symptoms, patient-reported distress, patient-reported functional status, healthcare utilization (ED visit, hospitalization, IVU admission, treatment duration), and total cost of care. Patient symptoms, patient-reported distress, and patient-reported functional status are included in the Carevive system, which is embedded in the EHR. Healthcare utilization, cost to payer, patient cost responsibility, and survival will be evaluated using billing data. Data from the EMR and ePRO vendor will be linked to provide analysis of outcomes with consideration for patient demographics, cancer characteristics, and use of intervention. The data sources will included data from patients both retrospectively and prospectively, from 2012 - 2026. Data from patients who do not receive the intervention during this time will be used as control data and data from patients receiving the intervention will be used as intervention data.

7.2 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

7.2.1 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)).

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:

- 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.

7.2.3 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 if they are notified by clinical teams.

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.

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.

7.2.4 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.

7.3 UNANTICIPATED PROBLEMS

7.3.1 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.

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.

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.

8 STATISTICAL CONSIDERATIONS

8.1 STATISTICAL HYPOTHESES

- Primary Efficacy Endpoint(s): Service penetrance defined as proportion of patients approached who enroll in remote symptom monitoring.

- Secondary Efficacy Endpoint(s):

1. Proportion of Alerts Closed Within 48 Hours
2. % of Patients Completing ≥1 ePRO Survey
3. % of Expected ePRO Surveys Completed Per Patient
4. % of Surveys Completed of Surveys Sent to Patient: ePRO surveys are abstracted from the ePRO database including surveys completed
5. Symptom Trajectory: Proportion alerting for the population over 6 months
6. Number of ED Visits: Proportion with patients with an ED visit
7. Number of Hospitalizations: Proportion of patients hospitalized
8. Number of ICU Visits: Proportion admitted to the ICU
9. Total Cost of Care: total costs sent by UAB to payers

8.2 SAMPLE SIZE DETERMINATION

Power and sample size considerations: UAB and MCI see approximately 4000 and 2600 new patients per year, respectively. We anticipate approximately 35% of patients to be receiving chemotherapy, thus >2000 patients being eligible to participate in Home ePRO each year. We expect implementation will increase over 5 years. In Year 1, we anticipate at least 30% of patients to be approached (n=600) with increases by 10% each year to 70% (n=1400) at Year 5, for a total of 5000 patients over the duration of the funding period. As this is an opt-out program, we anticipate that 75% of patients will be willing to complete all Home ePROs if approached. Thus, we anticipate 3750 will enroll in Home ePRO, including 2250 at UAB and 1500 at MCI. Under these assumptions, the expected large sample size provides high power and precision. For expected 40% increase in patient participation between Year 1 and Year 5, the 99% confidence interval is 36%-44%. For the expected 75% participation in Years 1-5, the 99% confidence interval is 73%-77% (computations in PASS software).

8.2.1 GENERAL APPROACH

Primary data analysis will include descriptive statistics for baseline health system characteristics, participant demographics, and study outcomes. Descriptive statistics will be included for patients who are approached but choose not to participate in Home ePRO. Care will be taken to ensure that the collected data are as complete as possible. Chart review will be completed where EMR abstraction has missing data. Patterns and impact of missing data will be examined. We will examine differences in patient characteristics between those who participate and those who do not using bivariate measures of association (e.g., Cohen's d, Cramer's V). For patient outcomes, site and navigation team will be treated as fixed effects when needed, as all navigation teams will be included.

8.2.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

Primary analysis will be conducted using binomial logit models to estimate the service penetration proportions of interest. For example, a binomial model (events/trials syntax) will be fitted with coefficients for time (e.g. year: 1 through 5, as categorical), site, and an interaction between the two to estimate time trends for the percentage of eligible patients enrolled among those eligible, overall, and by site. Model-predicted means and inverse-link transformations will be used to estimate the proportions of interests (or differences) and respective confidence intervals.

8.2.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Secondary analysis for patient outcomes will use logit models to evaluate the association between penetration outcomes and pertinent characteristics including race, rurality (estimated using rural-urban commuting area codes), and using non-linear effects (e.g. splines) as appropriate, driving distance from cancer care site, and socio-economic disadvantage status (estimated using the area deprivation index). For clinician metrics, generalized linear mixed models with random effect for clinician team will be used to estimate the monthly response to alerts and time to response. A False Discovery Rate approach will be used to correct for multiple inference when appropriate (10% FDR).

Patient-reported outcomes and utilization trends will be described for all patients, for patients receiving Home ePRO, and for patients not receiving Home ePRO.

We will use generalized models to compare patients on RSM to historical controls for healthcare utilization and cost of care at 3 and 6 months. Additional subset analysis will be conducted by race and residence. Models will be adjusted for appropriate patient demographic and clinical characteristics. As a sensitivity analysis, we will use non-linear modeling (e.g., a Random Forest approach41) to estimate a propensity score (the probability of being a Home ePRO participant given the values of relevant patient characteristics) and use it to match Home ePRO participants with historical controls using radius matching. If needed, we will use matching with replacement in order to include as many Home ePRO patients as possible in the analyses. Given that cancer type will impact symptom burden and other outcomes, we will conduct the matched analysis for the whole sample and for common cancer types for which there will be sufficient numbers for statistical matching (breast, prostate, colon, lung, and ovarian cancer). To minimize the potential confounding effect of change or improvement of cancer therapy over time, we will restrict the pool of controls to patients initiating treatment up to 3 years before the implementation of Home ePRO intervention. Given this time restriction, it is possible that matching with replacement (i.e., a control patient could be matched with more than one ePRO patient) will be needed to include as many Home ePRO patients as possible. We will then use generalized linear or generalized linear mixed models, as appropriate, to conduct between-group comparisons on ePROs, healthcare utilization, and cost of care. For the survival analysis, we will recode and censor the survival time of the controls as appropriate to match the potential follow-up time of the Home ePRO patients. We will use time-to-event models (Cox proportional hazards or frailty models, as appropriate) to estimate and provide inferences on survival differences. Regression on the restricted mean survival time and Kaplan-Meier curves will also be produced. If matching with replacement was conducted, then cluster-level bootstrapping (clusters indicated by the individual control patients) will be used to provide inference on these procedures. A False Discovery Rate approach will be used to correct for multiple inference when appropriate (10% FDR).

8.2.4 SAFETY ANALYSES

Any safety events that are identified related to conduct of the research or notifications of adverse events related to remote symptom monitoring. There is not capture of adverse events related to cancer or treatment for cancer.

8.2.5 BASELINE DESCRIPTIVE STATISTICS

Descriptive statistics will include counts, frequencies, means, and standard deviations.

9 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

9.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

9.1.1 INFORMED CONSENT PROCESS

A waiver of informed consent will be obtained for the secondary data analysis that assessed process and patient outcome measures.

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 the Institutional Review Board (IRB), will provide the reason(s) for the termination or suspension.

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

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.

9.1.5.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 5 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