Single-Use Negative Pressure Wound Therapy for Free Flap Donor Sites

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Sponsor: University of Alabama at Birmingham

National Clinical Trial (NCT) Identified Number: NCT03340025

Version Number: v.1.0

21 November 2017

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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 participants. 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 participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant 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 participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Single-Use Negative Pressure Wound Therapy for Free Flap Donor Sites
Study Description:	This study will be a single-center, randomized, parallel-assignment clinical trial to assess the efficacy of using single-use negative pressure wound therapy (NPWT) devices on free flap donor sites. Subjects will be randomized to one of two treatment arms (NPWT single-use device vs traditional wound dressing).
Objectives:	Primary Objective: To assess the progression of wound healing from Baseline through 30 days.
Endpoints:	Primary Endpoint: Progression of wound healing, as measured by comparison of photographs of all subject wounds taken at post-operative Day 5, post-operative Day 14-21, and post-operative Day 30. Percentage skin graft take will be evaluated on Day 30 by blinded, independent raters.
Study Population:	It is anticipated that 20 subjects will be enrolled in this protocol. Potential subjects will be male or female adults over the age of 18 from the United States who are undergoing head and neck surgery requiring reconstruction with a free flap, for which the donor site will be covered with a split-thickness skin graft (i.e., radial forearm free flap or fibula free flap).
Phase:	N/A
Description of Study Intervention:	*Treatment group:* PICO Single Use Negative Pressure Wound Therapy System, a Class II negative pressure wound therapy powered suction pump *Control group:* xeroform gauze, a traditional surgical dressing of xeroform gauze and padding
Study Duration:	Approximately 12 months
Participant Duration:	Approximately 14 days

1.2 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Screening Day -7 to -1	Baseline Day of Surgery Day 0	POD 5 Day 5 (±2)	POD 14 Day 14 (±7)	POD 30 Day 30 (±7)	End of Study
Informed consent	X					
Demographics	X					
Medical history	X					
Randomization		X				
Study intervention		X				
Wound photograph			X	X	X	
Blinded assessment of wound photographs						X
Concomitant medications	X	X	X	X	X	
Adverse events		X	X	X	X	

2 INTRODUCTION

2.1 STUDY RATIONALE

Various management options for free flap donor sites that require split thickness skin grafting exist. None has proven superior from both a patient care and a cost standpoint. Major complications occurring at these surgical sites include wound breakdown, tendon exposure, and loss of function. We seek to investigate the use of the PICO single-use negative pressure wound therapy device in these surgical sites and determine if it can yield superior results to simpler methods.

2.2 BACKGROUND

Many studies have addressed the use of negative pressure wound therapy (NPWT) in free flap donor sites with mixed results. It is well established that NPWT is safe and causes no harm, and no delay in healing. A previous study performed at UAB showed that NPWT in complex Head & Neck Surgery reconstruction is safe, including free flap donor sites. There have been studies that state the rate of tendon exposure is lower with NPWT in free flap donor sites, and studies that conclude there is no difference in complication rates. Current clinical practice is varied, often within a single institution.

While no studies of NPWT in free flap donor sites have noted inferior results with its use, a primary reason cited for not using it is cost. Traditional NPWT using canister-based vacuum devices adds significant cost. The PICO single-use NPWT device (Smith & Nephew) is a relatively inexpensive, low-profile dressing that does not require attachment to an external canister. It is battery-powered and disposable. Empiric use on our patients undergoing split-thickness skin-grafting to free flap donor sites shows good results with minimal intra-operative effort compared to traditional bandaging. We would like to prospectively investigate the use of this low-cost NPWT device and compare it directly to the traditional post-op dressing method.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

All of the devices to be used in this study are FDA-cleared, commercially available, and will be used for their approved indications.

- *Risks associated with the PICO NPWT device*: Per the device labeling, PICO not intended for use with complex wounds with extensive undermining or tunneling, or wounds that exceed 25% of the dressing pad area. It is not intended for use with patients with malignancy in the wound bed or margins; previously confirmed or untreated osteomyelitis; non-enteric and unexplored fistula; use on necrotic tissue with eschar present; use over exposed blood vessels, nerves, or organs; exposed anastomotic sites. There is a small risk of superficial pain at the application site and with removal of this device.

- *Risks associated with xeroform dressing:* Per the device labeling, xeroform petrolatum dressing is not labeled for use with third degree burns; as having an accelerating effect on the rate of wound healing or epithelization; as a long-term, permanent, or no change-dressing, or as an artificial (synthetic) skin; as a treatment or cure for any type of wound. There is a small risk of superficial pain with removal of this device.

2.3.2 KNOWN POTENTIAL BENEFITS

All of the devices to be used in this study are FDA-cleared and will be used for their approved indications.

- *Benefits associated with the PICO NPWT device*: Per the device labeling, PICO is indicated for patients who would benefit from a suction device (negative pressure wound therapy) as it may promote wound healing via removal of low to moderate levels of exudate and infectious materials. Appropriate wound types include chronic, acute, traumatic, subacute and dehisced wounds, partial-thickness burns, diabetic or pressure ulcers, flaps and grafts, and closed surgical incisions.
- *Benefits associated with xeroform dressing:* Per the device labeling, xeroform petrolatum dressing is intended for use as a primary contact layer in dressing wounds such as lacerations, skin graft recipient sites, newly sutured wounds, abrasions, and minor or partial thickness burns. It may also be used as an initial layer in dressing surgical wounds with light exudate.

3 STUDY DESIGN

3.1 OVERALL DESIGN

This study will be a single-center, randomized, parallel-assignment clinical trial to assess the efficacy of using single-use negative pressure wound therapy (NPWT) devices on free flap donor sites. The study duration is approximately 12 months and the subject duration is approximately 30 days.

The primary objective of this study is to assess the progression of wound healing from Baseline through 30 days.

There are 2 arms of the study:

1. *Treatment Group*: PICO Single Use Negative Pressure Wound Therapy System
2. *Control Group*: conventional dressing of xeroform gauze and padding

3.2 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.2.

The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally.

4 STUDY POPULATION

4.1 INCLUSION CRITERIA

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

1. Male or female, aged 18 or older
2. Able to consent for themselves
3. Undergoing reconstructive surgery requiring split-thickness skin graft coverage of a free flap donor site (i.e., radial forearm free flap or fibula free flap)

4.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Less than 18 years of age
2. Unable to consent for themselves
3. Undergoing reconstructive surgery that does not require split-thickness skin graft coverage of a free flap donor site

4.3 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) may not be rescreened.

4.4 STRATEGIES FOR RECRUITMENT AND RETENTION

Patients who have presented to the UAB Department of Otolaryngology for evaluation and treatment of head and neck disorders requiring surgery. The Principal Investigator and sub-investigators have practices specifically designated for treating head and neck disorders, with potential for enrollment.

Subjects will be identified from individuals treatment by the investigators in their clinics. Potential subjects will be approached by the Principal Investigator or qualified research staff authorized to conduct the informed consent discussion during their regularly-scheduled clinic visit about participation in the study.

5 STUDY INTERVENTION

5.1 STUDY INTERVENTION(S) ADMINISTRATION

5.1.1 STUDY INTERVENTION DESCRIPTION

All study interventions are FDA-cleared, commercially available, and will be used in accordance with approved labeling. No modifications have been performed for this study.

Treatment Group
510(k) Number: K151436
Trade/Device Name: Pico Single Use Negative Pressure Wound Therapy System
Regulation Number: 21 CFR 878.4780
Regulation Name: Powered suction pump
Regulatory Class: Class II
Product Code: OMP

PICO Single Use Negative Pressure Wound Therapy System is a small, lightweight, portable suction device consisting of an electric motor driven, twin-diaphragm, vacuum pump connected to a super-absorbent, gentle adhesive dressing. The pump, dressing and secondary fixations strips are supplied sterile and single use. The dressing is applied to the wound and secondary fixation strips are placed over the outside edges to help hold the dressing in place. When the suction pump is turned on, air is pulled out of the dressing creating negative pressure and drawing excess fluid from the wound into the dressing. The pump is battery operated and is supplied with two AA lithium batteries which provide up to 168 hours (7 days) of battery life depending upon leak rate. The batteries can be replaced if required. The pump is programmed to stop working after 168 hours (7 days) of use and will not re-start after this time, even with new batteries. Negative pressure will not be applied at this point.

Control Group
510(k) Number: K152970
Trade/Device Name: Dynarex Xeroform Petrolatum Dressing
Regulatory Class: Unclassified
Product Code: FRO

The Dynarex Xeroform Petrolatum Dressing is a sterile, single use, non-adherent dressing consisting of non-woven absorbent gauze saturated with Xeroform with 3% Bismuth Tribromophenate in a petrolatum blend. Packaged in paper metalized chevron pouches and available in several sizes.

5.2 MEASURES TO MINIMIZE BIAS: RANDOMIZATION

Subjects will be randomized 1:1 (parallel assignment) into the two treatment groups. The next subject to be randomized into a trial will receive the treatment corresponding to the next free number in the

randomization schedule. The appropriate number and associated treatment for the next subject will only be allocated when entry of that subject to the randomized part of the trial has been confirmed.

5.3 STUDY INTERVENTION COMPLIANCE

Define how adherence to the protocol (e.g., administration of study intervention, use of device,) will be assessed, and verified (if applicable, e.g., plasma assays, electronic monitoring devices, daily diaries). Include a discussion of what documents are mandatory to complete (e.g., participant drug log) and what source documents/records will be used to calculate study intervention compliance.

For both the Treatment Group and the Control Group, the dressings will remain in place until post-op day (POD) #5. Following dressing removal on POD #5, participants in both groups will be given identical wound management instructions. Photographs of each participant's healing wound will be obtained on POD #5 (+1 day) and on their first post-op clinic visit, approximately POD #14-21, and at POD #30 (+7 days). Participants who do not come to their designated follow-up appointments will be dropped from the dataset.

6 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

6.1 DISCONTINUATION OF STUDY INTERVENTION

Discontinuation from the study intervention (PICO vs xeroform dressing) does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- Wound photograph
- Assessment of adverse events
- Assessment of concomitant medications

6.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a participant 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 participant

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 participant 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 participant fails to return to the clinic for a required study visit:

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

Subjects aged 18 or older who are undergoing surgery with reconstructive repair for a head and neck condition as part of routine clinical care will be approached to participate in the study. Subjects screened and enrolled will follow the schedule of events provided in Section 1.2. The following evaluations will be performed:

Screening (Day -7 to Day -1)

- Obtain written informed consent
- Obtain demographic information
- Obtain medical history
- Obtain concomitant medication information

Baseline/Day of Surgery (Day 0)

- Randomization into the Treatment Group or Control Group, as per measures outlined in Section 6.2
- Study device administration to subjects in both the Treatment Group and the Control Group
- Assessment of adverse events
- Assessment of concomitant medications

POD #5 (Day 5 +2)

- Photograph of wound healing
- Assessment of adverse events
- Assessment of concomitant medications

POD #14 (Day 14 +7)

- Photograph of wound healing
- Assessment of adverse events
- Assessment of concomitant medications

POD #30 (Day 30 +7)

- Photograph of wound healing
- Assessment of adverse events
- Assessment of concomitant medications

The wound photographs will be de-identified, and a 10x10 grid digitally overlain on each image. The de-identified images will be randomized and given to two independent raters for assessment of wound healing.

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 CLASSIFICATION OF AN ADVERSE EVENT

7.2.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant’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 participant'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".

7.2.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant 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.

7.2.3.3 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.

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 participant 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 participant is screened will be considered as baseline and not reported as an AE. However, if the study participant'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 investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

7.2.5 ADVERSE EVENT 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.

8 STATISTICAL CONSIDERATIONS

8.1 STATISTICAL HYPOTHESES

Primary Endpoint(s): Progression of wound healing, as measured by comparison of photographs of all subject wounds taken at post-operative Day 5, post-operative Day 14-21, and post-operative Day 30. Percentage skin graft take will be evaluated on Day 30 by blinded, independent raters.

8.2 SAMPLE SIZE DETERMINATION

Our statistics indicate that assuming an 80% graft take, the number of patients needed for an appropriately powered study (80%) would be 44 patients in each group; however, we plan to only recruit 20 participants total, making this more of a pilot study to see if it's worthwhile to pursue a larger, prospective randomized controlled trial, given the costs associated with the devices to be used in this study.

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 PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention.

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 participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants 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 participants 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 participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

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 participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants 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 participants
- 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

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. 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 sponsor.

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) the participants in this study. The clinical study site will permit access to such records.

The study participant'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 participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Department of Otolaryngology research office. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and 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.

Hardcopies of source document worksheets for recording data for each participant enrolled in the study.

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, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, 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 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
CFR	Code of Federal Regulations
CONSORT	Consolidated Standards of Reporting Trials
EC	Ethics Committee
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ISM	Independent Safety Monitor
MOP	Manual of Procedures
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
SOC	System Organ Class
SOP	Standard Operating Procedure
US	United States