Partnership to Establish a Practice Based Network to Assess for Head and Neck Cancers Using a Low-cost Portable Flexible Nasopharyngoscope – Optimization Phase

NIDCR Protocol Number: 22-136-E

NIDCR Grant Number: R01 DE028555

Principal Investigator: Walter Lee, MD

Grantee Institution: Duke University Medical Center

NIDCR Program Official: Amanda Melillo, PhD

Draft or Version Number: 8.0

March 13, 2023

NCT04905134

STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the International Council for Harmonisation guidelines for Good Clinical Practice (GCP) (ICH E6) and the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46). National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Principal Investigator or Clinical Site Investigator:

Signed: _____ Date: _____

Name: Walter Tsong Lee
Title: PI

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
CCSG	Cancer Center Support Grant
CFR	Code of Federal Regulations
CRF	Case Report Form
CRO	Contract Research Organization
DCI	Duke Cancer Institute
DSMB	Data and Safety Monitoring Board
DUHS	Duke University Hospital System
ENT	Ears Nose and Throat
FDA	Food and Drug Administration
FNS	Flexible Nasopharyngoscope
FWA	Federal-wide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HNC	Head and Neck Cancer
HLD	High Level Disinfection
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IRB	Institutional Review Board
iRIS	Electronic IRB software system
MOP	Manual of Procedures
N	Number (typically refers to participants)
NIDCR	National Institute of Dental and Craniofacial Research, NIH, Department of Health and Human Services
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PHI	Protected Health Information
PI	Principal Investigator
PO	Program Official, NIDCR, NIH
PRMC	Protocol Review and Monitoring Committee
PRMS	Protocol Review and Monitoring System
SAE	Serious Adverse Event/Serious Adverse Experience
SOC	Standard of Care

SOC	Safety Oversight Committee
SOP	Standard Operating Procedure
SC	Study Coordinator
US	United States

PROTOCOL SUMMARY

Title:

Partnership to Establish a Practice Based Network to Assess for Head and Neck Cancers Using a Low-Cost Portable Flexible Nasopharyngoscope – Optimization Phase

Précis:

The optimization phase of this study will be conducted at Duke University. The implementation phase will be done in Vietnam and conducted under a separate protocol. During optimization, direct comparison between the standard flexible nasopharyngoscope scope used in the US. with the new mobile flexible nasopharyngoscope (FNS) will be done to optimize the FNS design to be noninferior to the standard of care (SOC) exam. Any patient who meets clinical indication for a nasopharyngoscope exam is eligible for the study. If consent is given the subject will first undergo the "SOC" scope endoscopy. Then the FNS exam will be performed using the mobile device. A post-procedure survey will then be administered and completed by both the provider and subject. Post-procedure data will be collected in three areas: technical assessment (i.e. image, lighting, and steering), physician feedback (i.e. ease of use, image quality), and subject feedback (i.e. perceived pain). Data collected during optimization will inform of final adjustments needed to the mobile FNS device before it is used to conduct the implementation phase in Vietnam. A protocol amendment will be submitted to include details about the implementation phase in Vietnam before study activities begin there.

Objectives:

Optimize the low cost FNS by comparing to SOC scopes at Duke University Medical Center

We will compare the use and reliability of the FNS scope to SOC scopes available at Duke University Medical Center. This will include image quality to see structures, lighting, and steering mechanism. Key objectives include ease of use, image quality, and perceived pain. The technical and subjective feedback will optimize the device to gain efficiencies and improve tolerability. Success is considered to be that the FNS is overall non-inferior to the current SOC scopes.

The expected outcome is to have an optimized FNS scope for production and widespread implementation and use

Population:	Up to 50 subjects 18 years or older who meet clinical criteria to undergo a SOC endoscopic exam
Phase or Stage:	N/A
Number of Sites:	1 site
Description of Intervention:	The FNS is used for assessment of the entire upper aerodigestive tract by Ear, Nose, and Throat (ENT) doctors or otolaryngologists and is part of SOC in the USA. This scope is inserted through the nasal passages into the pharynx, enabling a full view of all areas at risk for Head and Neck Cancer (HNC). Study participation ends once the post intervention survey is completed.
Study Duration:	3 months
Subject Participation Duration:	About 30 minutes
Estimated Time to Complete Enrollment:	2 months

Recruitment: Adult subjects that will undergo SOC endoscopy at the Head and Neck Surgery and Communication Sciences clinic at Duke will be approached by their treating physician if they would be interested in participating in this study. If they are interested, the study team will approach them to review the written consent form. Once signed, the SOC procedure will take place followed by the study scope procedure. The physician will complete their portion of the post procedure survey and assess for adverse effects. The subject will complete a single question on the survey focused on comparing the pain from both procedures.

1 KEY ROLES AND CONTACT INFORMATION

Principal Investigator:	Walter T. Lee MD, MHS Professor & Chief of Staff, Department of Head and Neck Surgery & Communication Sciences Co-Director, Head and Neck Program, Duke Cancer Institute Chief, Division of Head and Neck Surgical Oncology Duke University Medical Center [redacted]
NIDCR Program Official:	Amanda Melillo, Ph.D. Chief, Integrative Biology & Infectious Diseases Branch Director, Oral Opportunistic Pathogens & Viral Disease Program National Institute of Dental and Craniofacial Research (NIDCR), NIH (*https://www.nidcr.nih.gov/*) [redacted]

Clinical Site Investigators:

Russel R. Kahmke, MD, MMCi, FACS
Assistant Professor of Surgery
Department of Head and Neck Surgery & Communication Sciences
Division of Plastic, Maxillofacial, & Oral Surgery,
Department of Surgery
Duke University Health System
[redacted]

Daniel Rocke, MD, JD, FACS
Associate Professor
Department of Head and Neck Surgery & Communication Sciences
Duke University Medical Center
[redacted]

Institutions:

Duke University Medical Center
[redacted]

Walter Lee, MD
[redacted]

Vivo Surgical Private Limited
[redacted]

Kevin Koh, MD, CEO and Founder
[redacted]

Other Key Personnel:

Leah Zullig, PhD
Associate Professor
Department of Population Health Sciences
Duke University Medical Center
215 Morris St.
[redacted]

Maragatha Kuchibhatla, PhD
Professor of Biostatistics and Bioinformatics
Duke University Medical Center
[redacted]

2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Head and neck cancers (HNC) are the 6th most common cancers worldwide, with an incidence of 550,000 patients/year and a mortality rate of 356,000 patients/year (International; Jemal et al., 2011). Most HNC occur in the upper aerodigestive tract, which includes nasopharyngeal, tonsil, tongue, hypopharyngeal and larynx (voicebox) cancers (**Figure 1**).

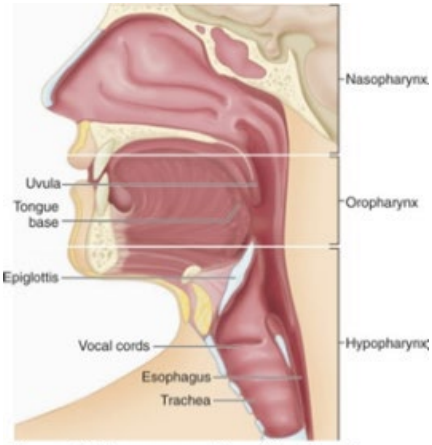


Figure 1: Upper aerodigestive tract

Proper examination of the head and neck region without specialized equipment and devices makes HNC difficult to diagnose at earlier stages.

A critical tool that has improved the examination of the areas where HNC can present is the FNS. The FNS is used for assessment of the entire upper aerodigestive tract by Ear, Nose, and Throat (ENT) doctors or otolaryngologists and is part of SOC in developed countries. This scope is inserted through the nasal passages into the pharynx, enabling a full view of all areas at risk for HNC. Furthermore, it allows for assessment of function of this area (e.g. vocal cord movement) that can provide important information for early detection of cancers. Currently, FNS systems at tertiary medical centers in the US cost around $10,000 and are large and heavy, limiting their use to a single room. **Figure 2** shows an example of a currently available system that includes a monitor, scope, light source, image processor, and printer.

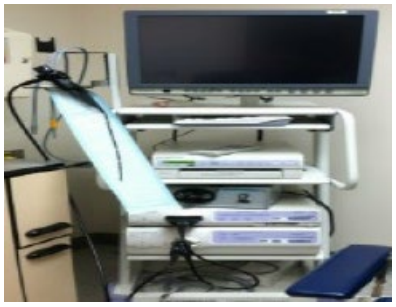


Figure 2: FNS System

This study seeks to develop a low cost FNS scope that can be used in low resource settings. The hope is that with an affordable device, this will improve the ability to screen for HNC. The optimization phase will compare this new prototype with standard SOC scopes used at Duke University.

2.2 Rationale

There is a rising global incidence of HNC in LMICs. Specifically, Vietnam has one of the highest incidences of HNC and the healthcare system is not meeting this need. Local provincial/district hospitals often lack scopes that provide adequate evaluations for patients. National/central hospitals have proper equipment for examinations, but are

overburdened by patients, many of which could have been cared for and treated locally if they could have been examined properly at local hospitals. A low cost FNS would significantly improve the ability of ENT doctors at these local hospitals to properly examine patients. Furthermore, training and equipping users at the district/provincial hospitals with this scope could improve clinical decisions as to which patients can be locally treated vs. referred. This could result in refocusing patient care burden at national specialty hospitals to conditions that truly need tertiary care (i.e. advanced HNC), rather than conditions that could be addressed at provincial/district hospitals.

Based on preliminary work, we have collected feedback from physicians on how to improve on our basic prototype. This includes providing consistent image quality to visualize the structures in the upper aerodigestive tract as well as improve lighting. Furthermore, the diameter of the scope is to be decreased to improve scope insertion and patient comfort. These factors are being incorporated into the first prototype to be used in this current clinical study. The goal is to optimize the low-cost scope as compared to the current SOC scope used at Duke.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

The SOC scope exam is done through the nasal cavity. Risks for the SOC include stiff neck, sore throat, temporary perceived difficulty breathing, bleeding, and minor damage to the lining of the airway. These are all considered very rare and self- limiting.

The risks to the subjects using the FNS include stiff neck, sore throat, temporary perceived difficulty breathing, bleeding, and minor damage to the lining of the airway. These are all considered very rare and self- limiting.

2.3.2 Potential Benefits

There are potential benefits to large parts of the developing world, if an affordable, easily portable scope proves clinically acceptable. There may be benefit for earlier detection of cancer or other lesions using the FNS in settings in which no scope device is available.

3 OBJECTIVES AND OUTCOME MEASURES

OBJECTIVES:

We will collect user feedback and reliability of the low-cost FNS scope as compared with the currently used SOC scope procedure. Collection of technical issues with the low cost FNS prototypes will also include steering, lighting, video, fogging, image capture.

Key objectives include comparisons between the SOC scope and FNS:

Primary
Ease of use
Compared with the first scope, how easy was the second scope to use?

Very Hard	Harder	same	Easier	Very Easy
1	2	3	4	5

.
Secondary
1) Image Quality
Rate the video quality of the first scope: (Poor) 1 2 3 4 5 (Excellent)

Rate the video quality of the second scope: (Poor) 1 2 3 4 5 (Excellent)

2) Perceived pain by subjects
Did you experience more, the same, or less pain/discomfort with the second scope compared with the first scope?

much more	about the same	much less
1	2	3

OUTCOME MEASURES

3.1 Primary

Objective	Brief Description/Justification of Outcome Measure	Outcome Measured By	Time Frame
Assess ease of use by end users between the SOC scope and FNS	We are comparing the ease of use between the FNS to the SOC scope. This will impact the design considerations and modification for the prototype optimization.	Compared with the first scope, how easy was the second scope to use? Very Hard 1 Harder 2 Same 3 Easier 4 Very Easy 5	Up to 2 months

3.2 Secondary

Objective	Brief Description/ Justification of Outcome Measure	Outcome Measured By	Time Frame
Assess image quality and subject pain	Comparison of image quality between the SOC scope and FNS as well as subject perception of pain between the two exams will help to inform modifications needed for prototype optimization.	image quality of each scope: rated 1(poor) to 5 (excellent) perceived pain by subjects between scopes: Much More 1 About the same 2 Much Less 3	up to 2 months

4 STUDY DESIGN

The Optimization Phase (Phase 1) Due to new regulatory restrictions in Vietnam, the optimization phase for Aim 1 will now be conducted at Duke University. This will allow us to obtain data from subjects and providers that will be helpful in determining if additional adjustments or improvements are needed to the FNS prototype. Direct comparison between the current approach using available SOC flexible scopes with the new approach using the low cost FNS will be made. Potential eligible subjects being seen in the Duke Head and Neck Surgery and Communication Sciences clinic meeting clinical indication for a SOC scope exam will be approached for the study. If consent is given, the subject will first undergo the "SOC" scope endoscopy. Then the FNS exam will be performed using the prototype. A post-procedure survey will then be administered and completed by both the provider and subject. Post-procedure data will be collected in three areas: technical assessment, physician feedback, and subject feedback**.**

The entire study procedure after consent takes about 5 minutes: ~one minute for the SOC scope procedure, ~one minute to change to the FNS scope, ~one minute for the FNS procedure, ~one minute to complete the study survey. We will have at least two low cost FNS to use. To allow for high level disinfection (HLD) between use, we will recruit 2 study participants in the morning clinic session, and 2 in the afternoon for a total of 4 participants per day.

Data will be collected using REDCap on a tablet to enable real time data collection. REDCap is a browser-based survey data collection platform. The data input tablet will be password protected and coded. Data will be stored in the REDCap database. Data will be collected after each FNS scope procedure and will include a technical assessment from the physician. This assessment includes ease of use, and quality of the image. Finally, the subjects will use a numeric scale to assess and compare pain experience between the two scope procedures. Collection of adverse events will also be via REDCap at this time.

The study participation is completed on the scope when survey information is collected. Data collection for each FNS prototype will involve a cohort of up to 50 subjects.

This technical and subjective feedback from subjects and providers will be used to optimize the device during the Optimization Phase. Each outcome measure as described in Section 3.1 and 3.2 will be compared between the SOC scope to the low cost FNS and used as a basis for modifications. For example, if the low-cost FNS image quality is noted to have lower ratings compared to the SOC scope due to inadequate lighting, modifications will be made to increase the light output for the next prototype.

The goal is to modify the prototype so that the outcome measures from the low cost FNS meet or exceed the outcome measures from the SOC scope. If this is the case, no

further prototypes will need to be performed for the optimization phase. Thus, the threshold for success will be noninferiority of the FNS compared to the SOC scope.

In addition to survey feedback, the FNS will have capacity to capture anonymized images of the upper aerodigestive tract such as the oropharynx, larynx, and nasopharynx. These will be collected and stored to a centralized image library. There will be no link to the subject, thus preventing loss of confidentiality.

5 POPULATION

5.1 Participant Inclusion Criteria

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

- Willing and able to provide signed and dated written informed consent
- Willing to comply with all study procedures and be available for the duration of the study
- Male or female, aged 18 or older
- Patients who clinically meet clinical criteria for SOC scope examination of the upper aerodigestive tract. This includes signs and symptoms such as dysphagia, nasal obstruction, neck mass, throat pain, and hoarseness.

5.2 Participant Exclusion Criteria

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

- Withdrawal of consent during the study duration
- Subjects who have complications from the SOC exam
- Anyone unable to undergo the SOC exam

5.3 Strategies for Recruitment and Retention

Optimization Phase: Based on our prior work, 20 patients are seen daily per provider within the HNC Clinic at Duke University. We have 2 full time surgeons and 2 part time surgeons that see patients. About 50% of these patients require a SOC scope procedure. It is estimated that up to 50% of these patients would be willing to participate in this study. Thus, our target of having up to 50 subjects to assess each scope prototype version in order to make improvements focused on the stated outcomes is feasible and can be accomplished within 2-3 weeks. Participating HNC providers will be trained on the study and use of device prior to start of subject recruitment.

Potential subjects will be identified by their HNC provider during a SOC visit. The provider will ascertain interest in study participation. If a potential subject expresses interest then a member of the study team will review eligibility and conduct the consent process prior to the SOC scope exam and start of study activities. If the subject is not able to tolerate or has complications from the SOC scope exam then he/she will be considered a screen failure.

5.4 Participant Withdrawal or Discontinuation from Study Procedures/Intervention

5.4.1 Reasons for Participant Withdrawal or Discontinuation from Study Procedures/Intervention

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

An investigator may discontinue an individual's participation in an intervention or withdraw an individual from the study if:

- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.
- Inability to complete the FNS exam (i.e., bilateral nasal obstruction preventing passing of the flexible FNS)

5.4.2 Handling of Participant Withdrawals from Study or Participant Discontinuation of Study Intervention

The reason for withdrawal will be solicited from the subject if they choose to stop the investigational scope exam and this will be recorded in the REDCap database. Replacement participants will be recruited until enrollment is complete. Data that is already collected will be included in the analysis and not destroyed.

5.5 Premature Termination or Suspension of Study

This study may be 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 the investigator, funding agency (NIDCR), and regulatory authorities. The principal investigator will also promptly inform the IRB and NIDCR and will provide the reason(s) for the termination or suspension.

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

- Determination of unexpected, significant, or unacceptable risk to participants.
- Insufficient adherence to protocol requirements.
- Data that are not sufficiently complete and/or evaluable.
- Determination of futility.

6 STUDY INTERVENTION

6.1 Study Procedural Intervention(s) Description

A low-cost, mobile, FNS that could be used in low-resource settings was designed in 2011 by the PI and collaborators. The FNS is used for assessment of the entire upper aerodigestive tract by Ear, Nose, and Throat (ENT) doctors or otolaryngologists and is part of SOC in developed countries. This scope is inserted through the nasal passages into the pharynx, enabling a full view of all areas at risk for HNC.

This study will test a low cost FNS prototype based on one used in preliminary work (Figure 4). It has a self-contained monitor as well as replaceable batteries. There is an LED light in the articulating tip.
The new prototype will be built by Vivo Surgical and addresses many of the barriers to the implementation of the technology, and in consideration of aspects identified by physicians as being of particular importance. All modified and updated prototypes will be submitted to the IRB at Duke, Approval for use will be required prior to any clinical use.

Figure 4: FNS prototype with LED lighted articulating tip and attached user monitor.

The protective sheath covering developed under the supplemental grant will be used once it is ready for use (refer to separate COVID19 sheath sub-study document).

6.2 Administration of Procedural Intervention

The FNS will be used only by medical providers in Head and Neck Surgery at Duke. This procedural intervention will be only administered during a clinic visit. The participation is considered complete once the subject leaves the clinic visit. The actual duration of the FNS procedural intervention is estimated to last about 1 minute.

6.3 Procedures for Training of Clinicians on Procedural Intervention

Training will occur prior to the recruitment of subjects and initiation of study activities. Training sessions, led by the PI – Dr. Walter Lee will include details on the operation, cleaning, and care of the scopes. The clinicians for the optimization phase are faculty and are familiar with using a flexible scope.

6.4 Assessment of Clinician and/or Participant Compliance with Study Procedural Intervention

The 9 steps of the intervention FNS protocol are below.

1. Confirm understanding of procedure and subject consent. Confirm newly disinfected scope is being used.
2. Lubricate the FNS tip with gel and wipe FNS tip as needed to obtain clear image. Check mobility of FNS tip.
3. Place scope into nares with direct vision then look at screen.
4. Insert through nasal cavity being careful not to apply pressure on the nasal septum.
5. Assess nasal cavity, nasopharynx. Document any clinical findings per routine care practices.
6. Direct tip to make bend at nasopharynx and have subject breathe through the nose. This relaxes soft palate and opens airway.
7. Assess oropharynx by having subject protrude tongue. Assess larynx and hypopharynx by having subject phonate and sniff and swallow. Document and clinical findings per routine care practices.
8. Straighten tip and withdraw scope.
9. Immediately send scope for HLD per SOP. Complete study survey questions and assessment of SAE.

7 STUDY SCHEDULE

7.1 Enrollment/Baseline

- Obtain and document consent from participant on study consent form.
- Verify inclusion/exclusion criteria.
- Administer the SOC scope then FNS study intervention.
- Administer post procedural surveys:
    - Provider survey
    - Subject survey

8 STUDY PROCEDURES/EVALUATIONS

8.1 Study Procedures/Evaluations

The Study procedure includes the following:

AIM 1: FNS scope procedure

Post procedure survey

The FNS procedure has been described in section 6.4.

All surveys will be recorded via REDCap. This will be immediately completed by a study investigator and also the subject (as indicated).

(Surveys can be found under supplemental materials section of the protocol)

9 ASSESSMENT OF SAFETY

This study involves optimization of a low cost FNS. This is considered a nonsignificant risk investigational device by the FDA (21 CFR 874.4760 - Class II device). The risks are rare and include: stiff neck, sore throat, temporary loss of voice, temporary perceived difficulty breathing, bleeding, and minor damage to the lining of the airway. These are all self-limiting.

Prior to use in subjects, all study investigators will demonstrate competency in the FNS exam and study procedures. Only certified ENT surgeons listed as key personnel with the IRB will be performing the FNS exam. Manual HLD will be performed with Revital-Ox RESERT, a 2% Accelerated Hydrogen Peroxide solution, per manufacture instructions for use

After each study FNS procedure, the study investigator will record any observed adverse events. If there are adverse events, the subject will be observed until stabilization of the event has occurred. These are recorded real time to the REDCap database. If there are AE or unanticipated problems (UPs), the PI (WTL) will be notified via email.

The optimization phase of this study will be conducted at Duke University Medical Center and will require safety monitoring and oversight. The Duke study team will review safety information in real time as data are collected, as well as a monthly basis. Adverse events will be reported as outlined in the sections below.

9.1 Specification of Safety Parameters

Unanticipated problems (UPs) will be recorded in the data collection system (REDCap) and must be reported to the IRB and NIDCR in accordance with Duke IRB-defined timeline for reporting policy. An Adverse Event must be reported to the IRB if it: (i) is more likely than not related to study activities; and (ii) represents a new risk; and (iii) is unanticipated. In addition, an expected event that is occurring at a frequency or intensity greater than originally anticipated must be reported to the IRB.

UPs include incidents, experiences, and outcomes that are not adverse events, as well as a subset of adverse events. This study will follow Duke IRB policy for reporting other events to the IRB.

All serious adverse events (SAEs) that are also determined to be UPs will be reported to NIDCR and the IRB concurrently, for assessment by the NIDCR Medical Monitor.

Determining whether a particular adverse event is unexpected by virtue of an unexpectedly higher frequency can only be done through an analysis of appropriate data on all subjects enrolled in the research. If the investigator determines that an adverse event is not an unanticipated problem, but the NIDCR Medical Monitor subsequently determines that the adverse event does represent an unanticipated problem (for example, due to an unexpectedly higher frequency of the event), the NIDCR Medical Monitor will report this determination to the investigator, and such reports must be promptly submitted by the investigator to the IRB.

9.1.1 Unanticipated Problems

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

- unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research ("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.

9.1.2 Adverse Events

An adverse event is any untoward or unfavorable medical occurrence in a human subject, including any symptom temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

9.1.3 Serious Adverse Events

A serious adverse event (SAE) is one that meets one or more of the following criteria:

- Results in death
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred)
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability or incapacity
- An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

9.2 Time Period and Frequency for Event Assessment and Follow-Up

The PI and/or study team will record all events occurring any time after informed consent is obtained until the subject leaves the clinic. Subjects will only be allowed to leave the clinic once resolution of the event or patient stabilization occurs. This is adequate for the following reasons: 1) trained physicians skilled with endoscopic examinations are present to conduct the procedure and observe patients, 2) incidence of adverse events is rare, and 3) direct visualization of the placement of the scope will occur, thus preventing adverse events.

9.3 Characteristics of an Adverse Event

Each event will be recorded on an appropriate case report form that includes assessment of the characteristics defined below. These characteristics, along with the frequency of an event's occurrence, will be considered in determining if the event is a UP.

9.3.1 Relationship to Study Intervention

To assess relationship of an event to study intervention the following guidelines are used:

1. Related (Possible, Probable, Definite)
    a. The event is known to occur with the study intervention, and/or
    b. There is a temporal relationship between the intervention and event onset and/or
    c. The event abates when the intervention is discontinued, and/or
    d. The event reappears upon a re-challenge with the intervention.
2. Not Related (Unlikely, Not Related)
    a. There is no temporal relationship between the intervention and event onset, and/or
    b. An alternate etiology has been established.

9.3.2 Expectedness

The Study PI and/or study-appointed, clinically/medically responsible individual will determine whether an 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 intervention.

9.3.3 Severity of Event

The following scale will be used to grade adverse events:

1. Mild: no intervention required
2. Moderate: minimal, local, or non-invasive intervention indicated
3. Severe: significant symptoms requiring invasive intervention; subject seeks medical attention

9.4 Reporting Procedures

9.4.1 Unanticipated Problem Reporting

Incidents or events that meet the OHRP criteria for unanticipated problems require the creation and completion of an unanticipated problem report form. OHRP recommends that investigators include the following information when reporting an adverse event, or any other incident, experience, or outcome as an unanticipated problem to the IRB:

- appropriate identifying information for the research protocol, such as the title, investigator's name, and the IRB project number;
- a detailed description of the adverse event, incident, experience, or outcome;
- an explanation of the basis for determining that the adverse event, incident, experience, or outcome represents an unanticipated problem;
- a description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem.

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

- Immediately (within 24 hours) upon learning of an unanticipated study-related death, study personnel will notify the IRB via phone or e-mail by providing a brief summary of the event. Then, within 1 week (five business days), study personnel will send to the IRB a Safety Event submission in the eIRB.
- All unanticipated problems should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within one month of the IRB's receipt of the report of the problem from the investigator.

All unanticipated problems will be reported to NIDCR concurrently with reporting to the IRB. These reports will be made to NIDCR's centralized reporting system via the CROMS contractor. Additional reporting instructions can be found in the MOP.

9.4.2 Serious Adverse Event Reporting

The study's clinically responsible individual will complete a Serious Adverse Event Form and submit via fax or email within the following timelines:

- For a reportable serious adverse event, study personnel will notify the IRB within five business days of the investigator becoming aware of the event. Study personnel will send a Safety Event submission in the eIRB.
- For any other problem or event requiring prompt reporting to the IRB, within ten business days of the investigator becoming aware of the event, study personnel will send to the IRB a Safety Event submission in the eIRB.

All SAEs will be followed until resolution or stabilization.

9.5 Halting Rules

Subsequent review of serious, unexpected, and related AEs by the Medical Monitor, Data and Safety Monitoring Board (DSMB), IRB, the sponsor(s), or relevant local regulatory authorities may also result in suspension of further study interventions/administration of study product at a site. The study sponsor(s) retain the authority to suspend additional enrollment and study interventions/administration of study product for the entire study, as applicable.

Examples of findings that might trigger a safety review are the number of SAEs overall, the number of occurrences of a particular type of SAE, severe AEs/reactions, or increased frequency of events.

10 STUDY OVERSIGHT

Dr. Lee, Dr. Koh and Dr. Tan will have monthly meetings to assess progress and FNS feedback from end users.

The Advisory Board for this project is comprised of leaders in biomedical engineering, global health, and device development. The role of the advisory board will include advising regarding optimizing the prototype within the specified time period of 3 months. Dr. Walter Lee (PI, Duke University), and Kevin Koh (Vivo Surgical) will have formal meetings with the advisory board twice per year.

In addition to the PI's responsibility for oversight, study oversight will be under the direction of the Specialized Technology and Devices for Head and Neck Cancers (STAND) Data and Safety Monitoring Board (DSMB), who is composed of members with expertise in Head and Neck Squamous Cell Carcinoma and imaging, bioethics/health policy, practice-based research, and biostatistics. The DSMB will meet regularly, at an interval to be determined, to assess safety and efficacy data, study progress, and data integrity for the study. Per instructions given by the DSMB, safety reports will include the grades of adverse events and a summary of changes to the protocol, if there are any. The first DSMB safety report will be submitted three months following the start of the study. If safety concerns arise, more frequent meetings may be held. The DSMB will operate under the rules of an NIDCR-approved charter that will be approved at the organizational meeting of the DSMB. At this time, most data elements that the DSMB needs to assess will be clearly defined. The DSMB will provide recommendations to the NIDCR.

11 CLINICAL SITE MONITORING

The sponsor-investigator or principal investigator (PI), and Duke Cancer Institute (DCI), through the PRMS and PRMC, will monitor this clinical research study. For internal review, the sponsor-investigator or PI will continuously monitor and tabulate adverse events. The study team will make reports to the Duke University Hospital System (DUHS) Institutional Review Board (IRB). If an unexpected frequency of Grade III or IV events occur, depending on their nature, action appropriate to the nature and frequency of these adverse events (AE) will be taken. This may require a protocol amendment or potentially study closure. The study sponsor-investigator or PI will also continuously monitor study conduct, data, and safety to ensure:

- Interim analyses occur as scheduled.
- Stopping rules for toxicity and/or response are met.
- Risk/benefit ratio is not altered to subject detriment.
- Appropriate internal AE and outcomes monitoring is performed.
- Over-accrual does not occur.
- Under-accrual is addressed with appropriate amendments or actions.
- Data are being appropriately collected in a reasonably timely manner.

PRMS protocol review begins with the PRMC. PRMC new protocol reviews focus on scientific relevance, study design, biostatistical input adequacy, protocol prioritization, feasibility of study completion within a reasonable time frame and trial risk assessment. The sponsor-investigator or PI will abide by PRMC risk level assessment. PRMC also conducts annual scientific progress reviews on protocols open to enrollment and focuses on protocol prioritization, accrual, and scientific progress. The PRMC conducts reviews at the time of IRB annual renewals and maintains documentation in iRIS.

During the initial PRMC approval, the PRMC determines the monitoring risk level and frequency which will be commensurate with the type and level of intervention, phase, endpoints, degree of risk, size, and protocol complexity. The DCI monitoring team will conduct formal, independent monitoring according to the risk level and the PRMC monitoring plan until the study is closed to enrollment or subjects are no longer receiving study drug or other interventions that are more than minimal risk.

The DCI has determined this study to be “moderate risk/complexity”. Moderate Risk is defined as “Behavioral intervention, complex observational or sample/tissue or blood collection studies deemed more than minimal risk. These studies require a physical intervention with a participant”.

Per the DCI’s Data and Safety Monitoring Plan (DSMP), moderate risk studies undergo the following: A minimum of 10% of records to be reviewed every 6 months. Review may be more frequent based on findings in initial study review, enrollment, or at the request of the DCI Safety Oversight Committee or School of Medicine Clinical Quality Management Program.

Findings from monitoring visits, unexpected frequency of serious and/or unexpected toxicities, or other concerns may prompt additional monitoring. DUHS and DCI Leadership, PRMC, DCI Safety Oversight Committee (SOC), a sponsor, an investigator, or the IRB may also request additional monitoring visits.

The DCI monitoring team reviews informed consent adequacy, eligible patient enrollment, protocol-specified procedures and treatment implementation, data collection adequacy, and adverse event monitoring and reporting appropriateness. The DCI monitoring team presents final monitoring reports to the DCI SOC highlighting safety concerns and unresolved issues. The SOC, at a convened meeting, assigns an overall rating of satisfactory, marginal, or unsatisfactory to reflect the overall data quality, regulatory, consent, eligibility, study conduct, and AE reporting. Corrective action plans (CAPs) are developed, implemented, and evaluated as indicated. The SOC will notify the sponsor-investigator or PI and DUHS IRB when significant safety concerns are identified.

The SOC in conjunction with the DCI monitoring team conducts data and safety monitoring for DUHS sponsor-investigator or PI Phase I and II, therapeutic interventional oncology studies that do not have an independent Data Safety Monitoring Board (DSMB). These reviews occur at a minimum annually and possibly more frequently based on risk level. The SOC safety reviews include safety, data accuracy, enrollment status, stopping rules if applicable, accrual, toxicities, reference literature, and interim analyses as the sponsor-investigator provides. The SOC, at a convened meeting, assigns a “satisfactory” rating when adequate accrual with lack of excessive toxicity is present.

Clinical site monitoring is conducted to ensure that the rights of human subjects are protected, that the study is implemented in accordance with the protocol and/or other operating procedures, and that the quality and integrity of study data and data collection methods are maintained. In addition, monitoring for this study will be performed by NIDCR’s Clinical Research Operations and Management Support (CROMS) contractor. The monitor will evaluate study processes and documentation based on NIDCR standards and the International Conference on Harmonisation (ICH), E6: Good Clinical Practice guidelines (GCP).

Details of documented in a Clinical Monitoring Plan (CMP) developed by the CROMS contractor, in collaboration with the NIDCR Office of Clinical Trials and Operations Management (OCTOM) and the NIDCR Program Official. The CMP will specify the frequency of monitoring, monitoring procedures, the level of clinical site monitoring activities (e.g., the percentage of subject data to be reviewed), and the distribution of monitoring reports. Some monitoring activities may be performed remotely, while others will take place at the study site(s). Staff from the CROMS contractor will conduct monitoring activities and provide reports of the findings and associated action items in accordance with the details described in the CMP. Documentation of monitoring activities and findings will be provided to the site study team, the study PIs, OCTOM,

and the NIDCR. The NIDCR reserves the right to conduct independent audits as necessary.

12 STATISTICAL CONSIDERATIONS

12.1 Study Hypotheses

The study hypothesis is that a low cost FNS can be non-inferior to the SOC scope in terms of ease of use, image quality, and perceived pain.

12.2 Sample Size Considerations

Aim 1 is aimed at optimizing the FNS for its optimal functioning as explained in the recruitment described above.

Fixing alpha at 0.05, power at 80%, a sample size of 37 produces a two-sided 95% confidence interval with a width equal to 0.2 when the sample proportion of success is 0.9. The lower and upper confidence interval for this success rate of 0.9. is 0.76 and 0.96 respectively (PASS 16, 2018). Hence at the end of testing on 37 subjects, if the proportion who answer good outcomes as described in scenario 1 is between 0.76 and 0.96, phase one of the study is a success.

Power Analysis and Sample Size Software (2018). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass).

12.2.1 Safety Review

A review of adverse events will be done by the PI weekly. This will be done through review of the survey data. More frequent review may need to occur if SAE's will be identified and reported to the IRB within 5 days as stated in section 9.4.2

12.2.2 Efficacy Review

This study is an optimization study and seeks to optimize a low cost FNS for clinical use.

12.3 Final Analysis Plan

Statistical Analysis – Aim 1: Optimization Phase.

1. Outcome 1 (Primary): The primary outcome is ease of use comparison between the FNS to the SOC scope (score of 1 – 5, with 1 being very hard and 5 being very easy).
2. Outcome 2 (Secondary): Quality of the image (image quality score range 1-5, with 1 being poor and 5 being excellent).
3. Outcome 3 (Secondary): Perceived pain between the FNS to the SOC scope (pain score range of 1 – 3, with 1 being much more and 3 being much less).

Scenario 1:

Success of this first phase 1 (Aim 1) after evaluating 37 subjects is defined as - (1) at least 90% response of ease of use of second scope compared to first score to range from same to excellent (3 to 5); and (2) 90% responding to better video quality of second scope compared to first (score ranging from same to excellent (3 to 5); and (3) 90% responding to pain score of same or much less (2 or 3); In short, this phase is a success if 90% respond to same to excellent/much less on all 3 of the outcomes.

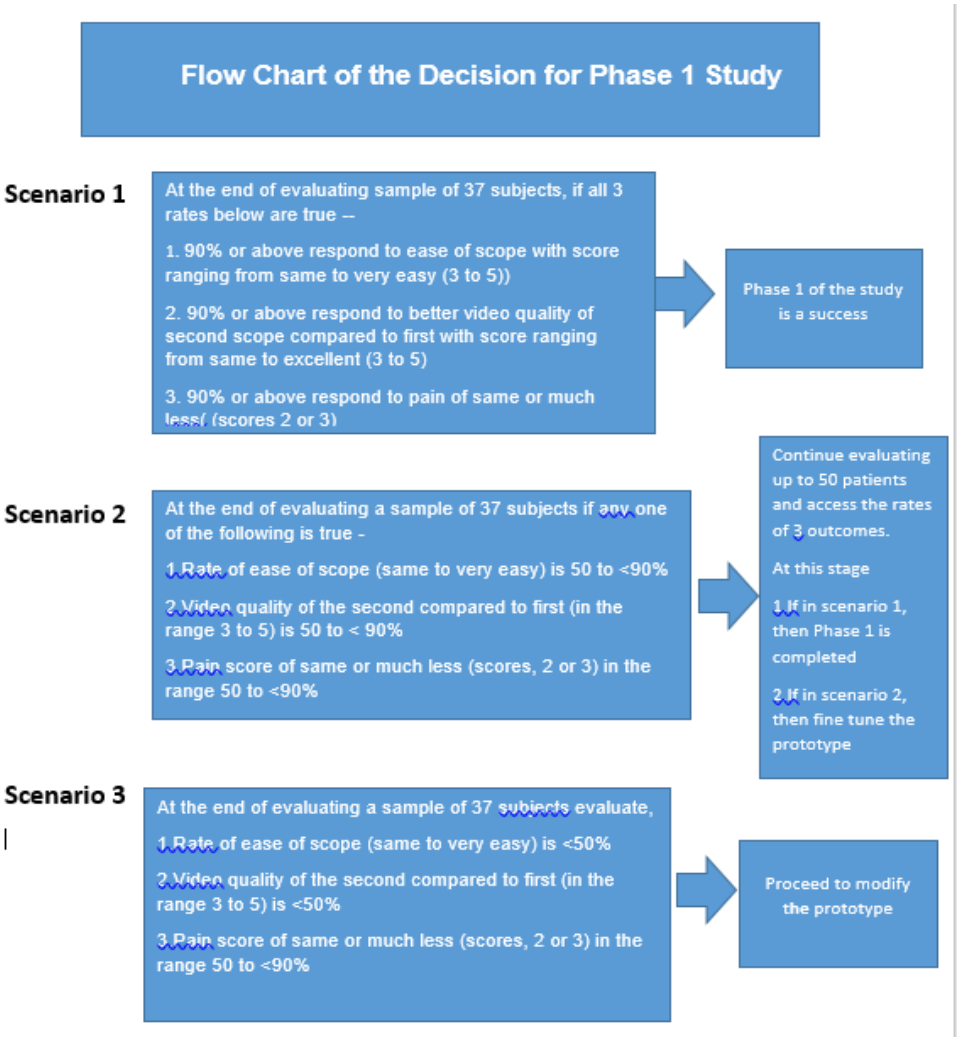
Scenario 2: If the rate is between 50 to < 90% for any three outcomes in a sample from 37, then the plan is to proceed recruiting more subjects until 50 are recruited. At 50 subjects, if in scenario 1 then phase 1 is a success and phase 1 is complete; if not, fine tune the prototype.

Scenario 3: If the rate is < 50% for any one of the 3 outcomes described above, then the plan is to proceed to fine tuning the prototype.

The primary outcome of ease of use of scope as reported by the physicians, will be examined between the two different scopes, at the simplest level, using paired Z-test if the scores (or transformed scores) are normally distributed or by using Wilcoxon test if the scores are non-normal.

The analysis for secondary outcomes of the change in the quality of the videos and pain will each be examined using paired Z-test, if the change (or transformed scores) is normally distributed or by Wilcoxon test if the change is non-normal. Assumptions of each of these tests will be examined. The significance of each of the outcomes will be examined at alpha = 0.05 The reliability of this instrument (using intra-class-correlation (ICC)) will be first assessed by using the data from the first 50 subjects. If ICC is < 0.9, we will include training component and necessary adjustment for the physicians.

See diagram below


Flow Chart of the Decision for Phase 1 Study
Scenario 1
At the end of evaluating sample of 37 subjects, if all 3 rates below are true --
1. 90% or above respond to ease of scope with score ranging from same to very easy (3 to 5))
2. 90% or above respond to better video quality of second scope compared to first with score ranging from same to excellent (3 to 5)
3. 90% or above respond to pain of same or much less((scores 2 or 3)
Phase 1 of the study is a success
Scenario 2
At the end of evaluating a sample of 37 subjects if any one of the following is true -
1 Rate of ease of scope (same to very easy) is 50 to <90%
2 Video quality of the second compared to first (in the range 3 to 5) is 50 to < 90%
3 Pain score of same or much less (scores, 2 or 3) in the range 50 to <90%
Continue evaluating up to 50 patients and access the rates of 3 outcomes.
At this stage
1 If in scenario 1, then Phase 1 is completed
2 If in scenario 2, then fine tune the prototype
Scenario 3
At the end of evaluating a sample of 37 subjects evaluate,
1 Rate of ease of scope (same to very easy) is <50%
2 Video quality of the second compared to first (in the range 3 to 5) is <50%
3 Pain score of same or much less (scores, 2 or 3) in the range 50 to <90%
Proceed to modify the prototype

13 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Source documents will include signed consent forms kept at the local study site, as well as the REDCap database which is web based. Study staff will maintain appropriate research records for this study, in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of participants. Study staff will permit authorized representatives of NIDCR and regulatory agencies to examine (and when required by applicable law, to copy) research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress, and data validity.

14 QUALITY CONTROL AND QUALITY ASSURANCE

PHI will be collected and stored on subjects enrolled at Duke. All potential subjects who are approached about study participation will be entered in a screening log. Those who agree to participate by providing written informed consent will be entered in the enrollment log and assigned a unique study ID number. Identifiers such as name, medical record number and date of study visit will be included in the enrollment log and the REDCap database. If electronic consent is obtained then email address will also be collected. Quality reviews will be done by the PI and study team on a weekly basis, and per the independent internal monitor as outlined in the CQMP. The PI and Study Coordinator (SC) will be responsible for correcting procedures that are not in compliance with protocol and quality control issues (correcting errors in data entry).

A kick-off meeting will be conducted to train study staff on the protocol and use of FNS device prior to start of study activities.

The Industry partner will assess the quality of the scopes prior and during usage. The industry partner will provide adequate support for repair or replacement as needed.

15 ETHICS/PROTECTION OF HUMAN SUBJECTS

15.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6, the Declaration of Helsinki, and the International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002).

15.2 Institutional Review Board

Review and approval of this protocol and the associated informed consent documents and recruitment materials by an appropriate IRB registered with the OHRP will be obtained. Duke University Health System IRB will be the IRB of record for the optimization phase. The FWA number assigned to Duke's IRB is FWA00009025, expiring 2/11/2027.

The protocol, informed consent form(s), and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is enrolled. Amendments to the protocol will require review and approval by the IRB and NIDCR before the changes are implemented in the study.

15.3 Informed Consent Process

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Written informed consent will be obtained by paper or electronic consent. An oral explanation of the study will be given to the potential subjects, and they will be asked to also read and sign the consent from. A copy will be provided to them. If electronic consent is obtained then an electronic copy will be automatically sent to the participants email address. Consent forms will be IRB-approved, and the participant is required to be able to read and review the document. The investigator or designee will explain the research study to the participant and answer any questions that may arise. The participant will sign the informed consent document prior to any study-related assessments or procedures. Participants will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time during the course of the study. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study.

The consent process will be documented in the electronic health record.

15.4 Exclusion of Women, Minorities, and Children (Special Populations)

There are no exclusionary criteria for the study population based on sex/gender, race, or ethnic background. As this is a focused device study on a new low-cost FNS, there is no scientific reason to exclude any subject by sex/gender, race of ethnic group, or pregnancy status. We are excluding children as head and neck cancers are very rare in this population.

15.5 Subject Confidentiality

Subject confidentiality is strictly held in trust by the investigators, study staff, and the study sponsor(s) and their agents.

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 study sponsor.

The study monitor or other authorized representatives of NIDCR may inspect all study documents and records required to be maintained by the investigator, including but not limited to source documents and survey responses for the study participants. The clinical study site will permit access to such records.

Certificate of Confidentiality

To further protect the privacy of study participants, the Secretary, Health and Human Services (HHS), has issued a Certificate of Confidentiality (CoC) to all researchers engaged in biomedical, behavioral, clinical, or other human subjects research funded wholly or in part by the federal government. Recipients of NIH funding for human subjects research are required to protect identifiable research information from forced disclosure per the terms of the NIH Policy (*https://humansubjects.nih.gov/coc/index*). As set forth in 45 CFR Part 75.303(a) and NIHGPS Chapter 8.3, recipients conducting NIH-supported research covered by this Policy are required to establish and maintain effective internal controls (e.g., policies and procedures) that provide reasonable assurance that the award is managed in compliance with Federal statutes, regulations, and the terms and conditions of award. It is the NIH policy that investigators and others who have access to research records will not disclose identifying information except when the participant consents or in certain instances when federal, state, or local law or regulation requires disclosure. NIH expects investigators to inform research participants of the protections and the limits to protections provided by a Certificate issued by this Policy.

NIH Data Sharing Policies

As described in section 17, it is NIH policy that the results and accomplishments of the activities that it funds should be made available to the public (see *https://grants.nih.gov/policy/sharing.htm*). PIs and funding recipient institutions will

ensure that all mechanisms used to share data include proper plans and safeguards to protect the rights and privacy of individuals who participate in NIH-sponsored research.

16 DATA HANDLING AND RECORD KEEPING

The investigators are 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. The investigators will maintain adequate case histories of study participants, including accurate case report forms (CRFs), and source documentation.

16.1 Data Management Responsibilities

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the investigator. All source documents must be reviewed by the study team and data entry staff, who will ensure that they are accurate and complete. Unanticipated problems and adverse events must be reviewed by the investigator or designee.

16.2 Data Capture Methods

The team will work with the research staff to develop a REDCap EDC that meets the data collection needs for the project. Data being collected for this project does not include identifiable information. The data will be stored in a HIPAA Compliant EDC. A member of the Clinical Data Management Team will have access to the data as outlined above for the duration of the project in order to oversee data security and data integrity on behalf of the Department and the Study Team.

16.3 Types of Data

Data containing PHI will be stored locally in the Duke REDCap database and the electronic screening/enrollment logs; PHI will include name, medical record number, email address, and date of visit. Survey data will include health care providers assessment of the prototype's 1) Ease of use and 2) quality of images. This will also include assessment of adverse events.

Furthermore, subjective pain comparison between the SOC and prototype scopes will be collected from the subject and study investigator via a tablet.

Data review and reports will occur at least twice a year or more frequently based on the final CQMP plan approved by the Duke School of Medicine's Office of Clinical Research from site visits by the independent medical monitor. Protocol and data review will occur during internal monitoring per the CQMP guidance document. Reporting enrollment schedule to the NIDCR will be determined by NIDCR and NIDCR appointed DSMB.

16.4 SCHEDULE AND CONTENT OF REPORTS

Data review and reports will occur at least twice a year from clinical site monitoring activities, as described under protocol section 11. Protocol and data review will also occur prior to DSMB reporting. The specific schedule or reporting will be determined by NIDCR and the NIDCR appointed DSMB.

16.5 Study Records Retention

Study records will be maintained for a minimum of six years following the completion of the study (closure with the IRB), or a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending, or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product (whichever is longer). These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

16.6 Protocol Deviations

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

These practices are consistent with investigator and sponsor obligations in ICH E6.

All deviations from the protocol must be addressed in study participant source documents and promptly reported to NIDCR and the IRB, according to their requirements.

17 PUBLICATION/DATA SHARING

This study will comply with all applicable NIH Data Sharing Policies. See *https://grants.nih.gov/policy/sharing.htm* for policies and resources.

NIH Public Access Policy

The NIH *Public Access Policy* requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to *PubMed Central* immediately upon acceptance for publication. This ensures that the public has access to the published results of NIH funded research.

18 LITERATURE REFERENCES

Abendstein, H., Nordgren, M., Boysen, M., Jannert, M., Silander, E., Ahlner-Elmqvist, M., Bjordal, K. (2005). Quality of life and head and neck cancer: a 5 year prospective study. *Laryngoscope, 115*(12), 2183-2192. doi:10.1097/01.MLG.0000181507.69620.14

Bellmunt, A. M., Roberts, R., Lee, W. T., Schulz, K., Pynnonen, M. A., Crowson, M. G., Shin, J. J. (2016). Does an Otolaryngology-Specific Database Have Added Value? A Comparative Feasibility Analysis. *Otolaryngol Head Neck Surg, 155*(1), 56-64. doi:10.1177/0194599816651036

Chapurin, N., Pynnonen, M. A., Roberts, R., Schulz, K., Shin, J. J., Witsell, D. L., Lee, W. T. (2017). CHEER National Study of Chronic Rhinosinusitis Practice Patterns: Disease Comorbidities and Factors Associated with Surgery. *Otolaryngol Head Neck Surg, 156*(4), 751-756. doi:10.1177/0194599817691476

Cheng, T.-M. (2014). Vietnam's Health Care System Emphasizes Prevention And Pursues Universal Coverage. *Health Aff (Millwood), 33*(11), 2057-2063. doi:10.1377/hlthaff.2014.1141

Cohen, J. (1988). *Statistical Power Analysis for the Behavioral Sciences*. Hillsdale NJ: Lawrence Earlbaum. Crowson, M. G., Schulz, K., Parham, K., Vambutas, A., Witsell, D., Lee, W. T., Langman, A. (2016). Meniere's Disease: A CHEER Database Study of Local and Regional Patient Encounter and Procedure Patterns. *Otolaryngol Head Neck Surg, 155*(1), 15-21. doi:10.1177/0194599815617752

Curran, G. M, Bauer, M., Mittman, B., Pyne, J. M., Stetler, C. (2012). Effectiveness-implementation hybrid designs: combining elements of clinical effectiveness and implementation research to enhance public health impact. *Med Care*, 50(3), 217-26. doi: 10.1097/MLR.0b013e3182408812.

Esteva, A., Kuprel, B., Novoa, R. A., Ko, J., Swetter, S. M., Blau, H. M., & Thrun, S. (2017). Dermatologist-level classification of skin cancer with deep neural networks. *Nature, 542*(7639), 115-118. doi:10.1038/nature 21056

Ghafoorian, M., Karssemeijer, N., Heskes, T., van Uden, I. W. M., Sanchez, C. I., Litjens, G., Platel, B. (2017). Location Sensitive Deep Convolutional Neural Networks for Segmentation of White Matter Hyperintensities. *Sci Rep, 7*(1), 5110. doi:10.1038/s41598-017-05300-5

Gibson, C. B. (2017). Elaboration, Generalization, Triangulation, and Interpretation On Enhancing the Value of Mixed Method Research. *Organizational Research Methods*, 20(2), 193-223. doi.org/10.1177/1094428116639133

Gupta, A., Keuskamp, D. (2018).Use and misuse of mixed methods in population oral health research: A scoping review. *Community Dent Health*. 30;35(2):109-118. doi: 10.1922/CDH_4250Gupta10.

Hanna, E. Y., Mendoza, T. R., Rosenthal, D. I., Gunn, G. B., Sehra, P., Yucel, E., & Cleeland, C. S. (2014). The symptom burden of treatment-naive patients with head and neck cancer. *Cancer*. doi:10.1002/cncr.29097

International, W. C. R. F. Cancer Statistics Worldwide. Retrieved from ***http://www.wcrf.org/cancer_statistics/world_cancer_statistics.php***

Jemal, A., Bray, F., Center, M. M., Ferlay, J., Ward, E., & Forman, D. (2011). Global cancer statistics. *CA Cancer J Clin, 61*(2), 69-90. doi:10.3322/caac.20107

Lawrentschuk, N., & Chamberlain, M. (2005). Sterile disposable sheath system for flexible cystoscopes. *Urology, 66*(6), 1310-1313. doi:10.1016/j.urology.2005.06.118

Lê Quang Cường, L. N. K., Khương Anh Tuấn, Trần Thị Mai Oanh, Dương Huy Lương, Nguyễn Thị Minh Hiếu, Trịnh Ngọc Thành, Hoàng Thu Thủy, Nguyễn Thị Thắng et al. (2011). Study on current situation of overcrowding, under-crowding in hospitals at levels and recommended solutions for improvement.

Lee, W. T., Witsell, D. L., Parham, K., Shin, J. J., Chapurin, N., Pynnonen, M. A., Schulz, K. (2016). Tonsillectomy Bleed Rates across the CHEER Practice Research Network: Pursuing Guideline Adherence and Quality Improvement. *Otolaryngol Head Neck Surg, 155*(1), 28-32. doi:10.1177/0194599816630523

Ministry of Health, V. (2016). *For People's Health Protection, Care and Promotion 2016-2020*. Hanoi, Vietnam.

NCCN National Pratice Guidelines in Oncology : Head and Neck Cancers. (2014). (2 ed.). NCCN.org.

Osthus, A. A., Aarstad, A. K., Olofsson, J., & Aarstad, H. J. (2011). Head and neck specific Health Related Quality of Life scores predict subsequent survival in successfully treated head and neck cancer patients: a prospective cohort study. *Oral Oncol, 47*(10), 974-979. doi:10.1016/j.oraloncology.2011.07.010

Parham, K., Chapurin, N., Schulz, K., Shin, J. J., Pynnonen, M. A., Witsell, D. L., Lee, W. T. (2016). Thyroid Disease and Surgery in CHEER: The Nation's Otolaryngology-Head and Neck Surgery Practice-Based Network. *Otolaryngol Head Neck Surg, 155*(1), 22-27. doi:10.1177/0194599815627641

PASS,2016, NCSS 11 Statistical Software (2016). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/ncss

Piker, E. G., Schulz, K., Parham, K., Vambutas, A., Witsell, D., Tucci, D., Lee, W. T. (2016). Variation in the Use of Vestibular Diagnostic Testing for Patients Presenting to Otolaryngology Clinics with Dizziness. *Otolaryngol Head Neck Surg, 155*(1), 42-47. doi:10.1177/0194599816650173

Powell, B. J., McMillen, J. C., Proctor, E. K., Carpenter, C. R., Griffey, R. T., Bunger, A. C., Glass, J. E., York, J. L. (2012). A compilation of strategies for implementing clinical innovations in health and mental health. Med *Care Res Rev*, 69(2),123-57. doi: 10.1177/1077558711430690.

Powell, B. J., Waltz, T. J., Chinman, M. J., Damschroder, L. J., Smith J. L., Matthieu M. M., Proctor, E. K., Kirchner, J. E. (2015). A refined compilation of implementation strategies: results from the Expert Recommendations for Implementing Change (ERIC) project. *Implement Sci*, 12, 10:21. doi: 10.1186/s13012-015-0209-1.

Schroy, P. C., 3rd, Wilson, S., & Afdhal, N. (1996). Feasibility of high-volume screening sigmoidoscopy using a flexible fiberoptic endoscope and a disposable sheath system. *Am J Gastroenterol, 91*(7), 1331-1337.

Vo, Q. T., Pham, D., Choi, K. J., Nguyen, U. T., Le, L., Shanewise, T., Lee, W. T. (2017). Solar-powered hearing aids for children with impaired hearing in Vietnam: a pilot study. *Paediatr Int Child Health*, 1-6. doi:10.1080/20469047.2016.1276119

SUPPLEMENTAL MATERIALS

Post-Procedural Survey By Clinician who performed the scope exam

(Provider questions once the SOC and study FNS exams are completed)**:**

TECHNICAL ASSESSMENT OF FNS

Were you able to complete the first scope procedure to your satisfaction?
1=no 2=somewhat 3=yes

Were you able to complete the second scope procedure to your satisfaction
1=no 2=somewhat 3=yes

Were you able to view all the structures of concern using first scope ? Y/N
If no, please explain:

Were you able to view all the structures of concern using second scope ? Y/N
If no, please explain:

Did the patient appear to have more, the same, or less discomfort with the second scope?

much more	about the same	much less
1	2	3

If much more: please describe why:

Were there technical issues with the second prototype scope? Y/N (if Yes, please explain below)

____ steering
____ lighting
____ video
____ fogging
____ image capture
____ other

Ease of use: Aim 1:

Compared with the first scope, how easy was the second scope to use?

Very hard	Harder	same	Easier	Very easy
1	2	3	4	5

If harder or very hard: please explain:

Quality of Images: Aim 1

Rate the video quality of the first scope: (Poor) 1 2 3 4 5 (Excellent)

Rate the video quality of the second scope: (Poor) 1 2 3 4 5 (Excellent)

Did the subject experience an AE: Y / N

If yes - please provide additional information below:
Name of adverse event: _____

Brief description of the problem or event:

Severity of adverse event (using scale below):

1. Mild: no intervention required
2. Moderate: minimal, local, or non-invasive intervention indicated
3. Severe: significant symptoms requiring invasive intervention; subject seeks medical attention

Is the adverse event related to study procedure?

1. **If related,** please specify: Possibly**,** Probably, or Definitely related
   a) The event is known to occur with the study intervention, and/or
   b) There is a temporal relationship between the intervention and event onset and/or
   c) The event abates when the intervention is discontinued, and/or
   d) The event reappears upon a re-challenge with the intervention.
2. **If not related**, please specify if unlikely related or Not Related)
   a) There is no temporal relationship between the intervention and event onset, and/or
   b) An alternate etiology has been established.

Is the problem/event unexpected? Y/N

Does the event meet the definition of a serious adverse event? Y/N

If yes, check criteria below:
A serious adverse event (SAE) is one that meets one or more of the following criteria:

1. Results in death

2. Is life-threatening (places the subject at immediate risk of death from the event as it occurred)
3. Results in inpatient hospitalization or prolongation of existing hospitalization
4. Results in a persistent or significant disability or incapacity

An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Outcome of adverse event: resolved or unresolved
Date of resolution:

For enrolled subjects

Pain Comparison: Aim 1-secondary objective

Did you experience more, the same, or less pain/discomfort with the second scope compared with the first scope?

much more	about the same	much less
1	2	3

CONSENT FORM FOR PARTICIPATING IN RESEARCH

Duke's IRB approved consent form will be provided separately