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Clinical Protocol

Version Number	**2.0**
Version Date	**November 5, 2019**
Amendment No.	**1**
Protocol Number	**PG-001**
Protocol Title	**Safety and Effectiveness Evaluation of the Peregrine™ Drivable ENT Scope for Office Endoscopy of the Paranasal Sinuses in Patients who underwent ESS**
NCT Number	**NCT04096482**

Approvals:

Site	**Sponsor**
_____	_____
Principal Investigator Date	Ehud Bendory Date
Signature	CEO
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A Study to Evaluate the Safety and Effectiveness Evaluation of the Peregrine™ Drivable ENT Scope for Office Endoscopy of the Paranasal Sinuses in Patients who underwent ESS

The Indications for Use for the investigational study devices are –

1) The Peregrine endoscopy system is intended to visualize the internal cavities of the ear, airways, nose and sinus cavities during diagnostic and therapeutic endoscope procedures.

Protocol Number: **PG-001**

Date: **November 5, 2019**

3NT Medical

22 Hamelacha St., POB 11384,

Rosh Ha'ayin, 4809169

Israel

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1 LIST OF ABBREVIATIONS

AE	Adverse Event
CRF	Case Report Form
CRS	Chronic Rhinosinusitis
CV	Curriculum Vitae
EC	Ethic Committee
ENT	Ear Nose and Throat
ESS	Endoscopic Sinus Surgery
FESS	Functional Endoscopic Sinus Surgery
ID	Identification
IRB	Institutional Review Board
RS	Rhinosinusitis
SAE	Serious Adverse Event
SOP	Standard Operating Procedures

2 SYNOPSIS

Protocol Number	PG-001
Protocol Title	Safety and Effectiveness Evaluation of the Peregrine™ Drivable ENT Scope for Office Endoscopy of the Paranasal Sinuses in Patients who underwent ESS
Participating Centers	Emory University, Atlanta, GA
Clinical Phase	Open, single-center, prospective
Investigational Study Device	Peregrine™ Drivable ENT Scope, by 3NT Medical
Study Procedures	Up to 30 Patients, out of which are at least 10 samples per each of the frontal, maxillary and sphenoid sinuses, who have had prior ESS and are scheduled for nasal endoscopy in the office as part of a routine post-operative office visit or due to recurrence of symptoms, will be evaluated with Peregrine Endoscope. The patients will attend the following visits: 1. Visit 1: Screening and Enrollment – as part of a regular office visit 2. Visit 2: Sinonasal endoscopy – evaluation with Peregrine and standard endoscopes Visits 1 and 2 can be combined into a single visit.
Study Population	Patients who have had prior ESS
Study Purpose	To assess the safety and effectiveness of Peregrine endoscope in patients in the office setting in terms of access into and visualization of the paranasal sinus anatomy, image quality, patient tolerability and clinical utility.
Study Endpoints	**Primary – Performance and Safety Endpoints:** • To compare visualization success rates of the paranasal sinus anatomy by Peregrine and by a standard endoscope used in the office setting. • Device related adverse events **Secondary – Performance Endpoints:** • To assess the adequacy of the image quality of Peregrine for endoscopy procedures in the office. • To evaluate patient tolerability and pain • To evaluate the impact of extended visualization by Peregrine on clinical workflow

Study Methods of Appraisal	**Methods:**
	
	During the study the subjects will be evaluated with:
	a. Mandatory – Peregrine Endoscope (the study device)
	b. Mandatory – A Standard 30° 4mm endoscope
	c. Optional – A Standard 70° 4mm endoscope
	d. Optional – A standard Flexible Endoscope
	
	Safety assessment
	
	Safety assessment will be based upon monitoring the Adverse device events, which will be collected throughout the procedures in which Peregrine was used.
	
	Performance assessment
	• Evaluation of ability of Peregrine and the comparison endoscope (a standard 30° endoscope) to access and visualize sinus anatomy (No. of successes divided by No. of attempts):
	  • Anatomic landmarks – Maxillary (ostium, anterior wall, lateral aspect, floor), Frontal (ostium, posterior wall, anterior wall, lateral recess), Sphenoid (ostium, sella, floor, lateral recess).
	  • Visualization success rates will be confirmed by direct visualization.
	  • Level of prior resection will be recorded – anterior or posterior ethmoidectomy, draf IIa, draf IIb, uncinectomy, antrostomy, maxillectomy, sphenoidotomy, dilation
	• Image quality – will be assessed through a yes/no statement regarding adequacy of Peregrine image quality for office endoscopy procedures, in comparison to the standard endoscope.
	• Patient pain and tolerability will be assessed through validated VAS for both Peregrine and the comparison endoscope.
	• Impact of Peregrine's extended visualization capability on clinical workflow will be evaluated through a series of questions regarding identification of pathology, evaluation of mucosa, change in medical management, need for additional CT scan, indication for revision surgery, etc.
	• Peregrine ease-of-use will be evaluated through a user questionnaire.
	• Irrigation (through Peregrine working channel) will be documented (performed/not performed), when performed.

Inclusion/ **Exclusion Criteria**	**Inclusion Criteria:** 1. A male or female patient who has had prior ESS and who is indicated for office endoscopy by the ENT specialist 2. Patient age: adult (>18 years old) 3. A patient who is able to understand the requirements of the study, is willing to comply with its instructions and schedules, and agrees to sign the informed consent **Exclusion Criteria:**

	1. Any medical disorder which in the investigator's judgment contraindicates the patient's participation 2. Pregnancy
Study Duration	Per Patient: up to 1 month A total of 6 months to recruit and treat up 30 patients.
Sample Size Calculations	The performance endpoint of the study will be to demonstrate that the Peregrine Endoscope will perform comparable to or better than a Standard 30° 4mm Endoscope, where a difference of 20% or more between visualization success rates will be considered to be statistically significant. Per protocol, a sub-group analysis of each of the different sinus cavities (i.e., Frontal, Maxillary and Sphenoid) will be used for power calculation. In order to maintain minimal Power 80% and Type I (=α) error of 5% to detect minimal differences of ±20%, a sample size of 7 samples is needed per sinus cavity. This number does not include an estimated 20-30% drop-out rate due to technical reasons unrelated to the device. Therefore, a sample size of 10 samples per each sinus cavity, and a total of 30 samples for all sinuses (total of up to 30 patients), will be recruited to the study.
Statistical Analysis Plan	Demographic and baseline characteristics will be summarized for all subjects included in the analysis. Continuous variables will be summarized using summary statistics (mean, standard deviation, median, range combined with 95% confidence interval calculations) and categorical variables will be summarized using counts and percentages. In particular, the following tests according to the parameters type are going to be performed: • Continuous parameters will be presented by the estimated value and calculation of 95% confidence intervals. In addition, the comparison will be by using the relevant Student's t-test. • Categorical parameters will be analyzed by Fisher exact test/ chi-square tests (in case of low observed frequencies). Tests will be two-sided in accordance to the hypothesis regarding the tested parameters, with a significance level of 0.05.

3 BACKGROUND

3.1 Nasal Endoscopy

Nasal endoscopy is a minimally invasive, diagnostic medical procedure and currently the most preferred initial method of evaluating medical problems affecting nose and sinuses such as nasal stuffiness and obstruction, sinusitis, nasal polyposis, nasal tumors, epistaxis, recurrent bouts of sneezing and rhinorrhea.

Nasal endoscopy allows a detailed examination of the nasal and sinus cavities not possible by standard examination such as anterior rhinoscopy using headlight or head mirror (1). It is more sensitive than computed tomography (CT) for the evaluation of accessible anatomy (2) and provides valuable information regarding persistent asymptomatic disease postoperatively. Most importantly, CT scan is associated with radiation exposure harmful to the patient and should be avoided if possible.

Areas visualized during endoscopy include the nasal cavity, inferior turbinate, inferior meatus, middle meatus, uncinate process, hiatus semilunaris, maxillary ostia, anterior ethmoidal bulla, nasofrontal recess, sphenoethmoidal recess, sphenoidal ostium, olfactory cleft and the nasopharynx (3)

Overall, the procedure is considered a very safe and a low-risk one (4). Occasionally, gagging, nosebleeds or coughing may occur as the endoscope is threaded through a nostril (5). Mucosal trauma and bleeding may rarely occur, particularly in susceptible patients with increased risk of bleeding, such as those receiving aspirin or other anticoagulant medications (i.e. Plavix®, Coumadin®, etc.). In addition, although not related to the endoscopic devices, adverse reactions to the topical decongestants or anesthetic provided prior to the procedure may occur prompting verification of patients' allergies prior to application.

Currently, nasal endoscopy can be performed with a flexible or rigid endoscope, typically after a topical decongestant and anesthetic are applied to the nasal mucosa. Notably, local anesthetic may not necessarily be beneficial when performing flexible nasal endoscopy, neither alone nor in combination with a vasoconstrictor. Water was suggested to be better than lubricant for Flexible Endoscope passage (6).

Reprocessing is an issue of concern, especially for Flexible Endoscope s where multiple steps were confirmed to be critical for reprocessing to be effective (7-9). High-level disinfection has been determined to be the minimum level of disinfection required, with several steps are important in all reprocessing techniques, including manual cleaning, leak testing, cleaning with an enzymatic agent, high-level disinfection, and drying with vertical storage (7).

3NT Medical Ltd. has developed the Peregrine™ Drivable ENT Scope, which offers the convenience of a single-use endoscope component coupled with performance characteristics of commercially available state-of-the-art reusable endoscopy systems. The single-use endoscope essentially removes concerns related to burdensome reprocessing techniques of a delicate tool required to achieve high-level of its disinfection.

The Peregrine Drivable ENT Scope is a minor modification to the Sinusway endoscopy system that was cleared by the FDA under K162916 and was tested and found to be safe and effective in various clinical studies.

4 OBJECTIVES

The objective of this study is to assess the safety and performance of Peregrine endoscope in patients in the office setting in terms of access and visualization of the paranasal sinus anatomy, image quality, patient tolerability and pain.

For this study, up to 30 patients who have had prior ESS and are scheduled for nasal endoscopy in the office, as part of a routine post-operative office visit or due to recurrence of symptoms, will be evaluated with Peregrine Endoscope. Access and visualization by an additional standard endoscope will be conducted and compared to Peregrine endoscope. Image quality of the Peregrine endoscope, Patient tolerability and pain, and the impact of Peregrine on clinical decision making will be evaluated.

4.1 Safety assessment

Safety assessment will be based upon monitoring the adverse device effects, which will be collected throughout the procedure.

All adverse events and serious adverse events will be reported in accordance with reviewing Ethics Committee /Institutional Review Board (IRB), FDA and Competent authority requirements.

4.2 Performance assessment

- To compare visualization success rates of the paranasal sinus anatomy by Peregrine and by standard endoscopes used in the office setting.
- To assess whether the image quality of Peregrine is adequate for endoscopy procedures in the office.
- To evaluate patient tolerability and pain.
- To evaluate Peregrine utility in clinical decision making.

4.3 Study End Points

Primary - Safety

All adverse device effects will be captured and summarized as defined in **Section-8.** Adverse device effects (type, frequency, severity) are expected to be similar to those reported in the literature for Nasal Endoscopy (section 8).

For this study, the Safety comparison with the data of Nasal Endoscopy reported in the literature will be descriptive with no statistical endpoints.

Primary – Performance

Evaluation of ability of Peregrine and the comparison endoscope to access and visualize sinus anatomy at the following landmarks:

- Maxillary (ostium, anterior wall, lateral aspect, floor)
- Frontal (ostium, posterior wall, anterior wall, lateral recess)
- Sphenoid (ostium, sella, floor, lateral recess)

Subjects will be evaluated with:

a. Mandatory – Peregrine Endoscope (the study device)
b. Mandatory – A Standard 30° 4mm endoscope
c. Optional – A Standard 70° 4mm endoscope
d. Optional – A standard Flexible Endoscope

- Visualization success rates, calculated as the No. of successes divided by the No. of attempts, will be confirmed by direct visualization.
- Representative images of the accessed anatomic landmarks will be recorded.
- Level of prior resection will be recorded – anterior or posterior ethmoidectomy, draf IIa, draf IIb, uncinectomy, antrostomy, maxillectomy, sphenoidotomy, dilation

Secondary - Performance

- Image quality – will be assessed through a yes/no statement regarding adequacy of Peregrine image quality for office endoscopy procedures, in comparison to the comparison device.
- Patient pain and tolerability will be assessed through validated VAS for both Peregrine and the comparison endoscope.
- Impact of Peregrine's extended visualization capability on clinical workflow will be evaluated through a series of questions regarding identification of pathology, evaluation of mucosa, change in medical management, need for additional CT scan, indication for revision surgery, etc.
- Peregrine ease-of-use will be evaluated through a user questionnaire.

Other Measurement – Performance and effectiveness

- Irrigation (through Peregrine working channel) will be documented (performed/not performed), when performed.
- To evaluate nasal cavity inflammation and sinuses inflammation using Lund Mackay CT score and Lund Kennedy Endoscopic scoring, if applicable.

As learning curve, each investigator participating in the study will use Peregrine in a cadaver specimen and/or anatomic model and/or during at least 1 procedure performed in the operating room (OR) under general anesthesia. The subject treated in the OR will be included in the safety analysis but not included in the efficacy analysis

5 DESCRIPTION OF PATIENT POPULATION

5.1 Patient Selection

Patients who have had prior ESS and are indicated for nasal endoscopy in the office (as part of a routine post-operative office visit or due to recurrence of symptoms)

5.2 Subject Enrollment

a) Patients who appear to be eligible will be asked if they would like to participate in this study.

b) Written informed consent will be obtained from each participating patient prior to collecting a patient history or other testing. The patient will be counseled concerning the research nature of this study, and the risks and possible benefits to participation. Participation is fully voluntary.

5.3 Inclusion Criteria

1. A male or female patient who has had prior ESS and who is indicated for office endoscopy by the ENT specialist
2. Patient age: adult (>18 years old)
3. A patient who is able to understand the requirements of the study, is willing to comply with its instructions and schedules, and agrees to sign the informed consent

5.4 Exclusion Criteria

1. Any medical disorder which in the investigator’s judgment contraindicates the patient's participation
2. Pregnancy

6 INVESTIGATION PLAN

6.1 Study Design

Type of Study

This is an open, single-center, prospective study in which the investigational device, the Peregrine Drivable ENT Scope, will be tested in a single group of adult patients, male or females.

The rationale behind this study is to show that the ability to visualize intra-sinus anatomic landmarks of the Maxillary, Frontal and Sphenoid sinuses is comparable to or better than the ability to visualize them with a Standard 70° 4mm Endoscope in the office setting; This study will evaluate the safety and performance of the Peregrine endoscope which enables intra-sinus visualization as a first step to assess potential benefits, ,such as minimizing CT scans and associated radiation exposure, change in medication regimen, referral to revision surgery, saving multiple office visits, and cost.

This study is proposed after completing a series of clinical cases with the Sinusway endoscopy system, (which is similar to the Peregrine Endoscopy system) which demonstrated that the system is safe and performed well to physician's satisfaction (detailed information on the studies is provided in the Investigator's Brochure).

Measures to Minimize Bias

Subjects shall constitute their own control group by comparing the ability to visualize intra-sinus anatomic landmarks and pain and tolerability between Peregrine and a standard endoscope in the same subject. For this reason, no randomization is necessary in this study.

6.2 Study Procedures

Visits 1: Screening and Enrollment

- Screening will take place at the day of procedure or within 1 day-30 days before the procedure as part of a regular office visit.
- Patients who potentially qualify for the study will be offered an Informed Consent to sign prior to further evaluation. Any patients who do not qualify will be exited from the study as screening failures and will not be included in the safety/effectiveness analyses.
- The following assessments will be performed before the procedure for each patient:
  - Medical history (including concomitant medications deemed relevant by the investigator)
  - Sino-Nasal outcome test (SNOT-22)
  - Vital signs – optional
  - CT scan – optional - as available in the patient file.
  - Nasal Cavity and sinuses inflammation score will be captured using the Lund Mackay CT
  - Compliance with inclusion/exclusion criteria
  - Patients found eligible to participate in the study during visit 1 will be scheduled to undergo nasal endoscopy evaluation with Peregrine.

Visit 2: Procedure

The procedure will be office endoscopy as part of a routine post-operative office visit or due to recurrence of symptoms. Visits 1 and 2 can be combined into a single visit.

- **Before the procedure:**
  - Eligible subject/s will attend the Medical Center at the day of procedure and will be inquired by the PI regarding changes to their health status since the screening visit. If at this point it is

determined that the patient ***does not*** meet all Inclusion and Exclusion criteria and cannot be treated, the patient will be exited from the study. These patients will be considered screening failures and will not be included in any of the safety or efficacy endpoint analyses.

- **Endoscopy:**
  1. Patients will undergo the procedure under local or topical anesthesia, at physician discretion.
  2. The Peregrine endoscopy system will be prepared for use per its instructions for use.
  3. Obligatory – the surgeon will attempt to visualize the pre-defined sinus anatomy landmarks with a standard 30° 4mm endoscope which will be recorded as success/failure, and an image of the anatomic landmarks visualized will be taken. Patient will be asked to score the endoscope for pain and tolerability.
  4. Obligatory – the surgeon will then attempt to visualize the pre-defined sinus anatomy landmarks with Peregrine endoscope which will be recorded as success/failure, and an image of the anatomic landmarks visualized will be taken. Patient will be asked to score Peregrine for pain and tolerability.
  5. Optional – the surgeon will have the option to attempt to visualize the pre-defined sinus anatomy landmarks with a standard 70° 4mm endoscope and/or a flexible endoscope which will be recorded as success/failure, and an image of the anatomic landmarks visualized will be taken. Patient will be asked to score the endoscope for pain and tolerability.
  6. Optional - irrigation of the nasal anatomy will be performed and recorded as Done/Not Done and which sinus was irrigated.
  7. The physician will answer a set of questions related to endoscope usability and utility in clinical decision making in comparison to the standard endoscope.
  8. The procedure will be recorded by site's AIDA system to enable the physician to perform assessments post procedure.

- **After the procedure:**

  - The patient will recover from the procedure according to center's common practice. Before the patient is dismissed, recording of AE, if any, will be performed. Patient will exit the study.

Visit 3: Telephone Follow-up visit

- Telephone Follow-up for safety assessment will be conducted by study personnel two weeks± 3 days following patient last study visit.
- In the absence of any on-going ADE's, the patient will exit the study and Exit Form will be completed.

6.3 Methods and Timing for assessments

Schedules of assessments are listed in **Table No. 1 below**.

Table 1: Study visit schedule			
Study Activities	**Visit I:** **Screening and Inclusion**	**Visit II:** **Procedure** **At day of screening or within 30 days post screening**	**Visit III:** **Telephone Follow-up** **Up to 2 weeks ± 3 days from visit II**
Informed Consent	X		
Demographic Data	X		
Medical History	X		
SNOT 22	X		
Concomitant medication related to sinus disease	X		
Physical Examination	X		
Vital Signs (optional)	X		
Inclusion/exclusion criteria	X		
CT scan (as available)	X (optional)		
Lund Mackay/Kennedy inflammation score	X		
Endoscopy with Peregrine and a standard Endoscope		X	
User questionnaire		X	
Patient tolerability and pain score		X	
AEs/SAEs		X	X
Patient Exit			X

7 STATISTICAL CONSIDERATIONS AND SAMPLE SIZE

Statistical Considerations

Demographic and baseline characteristics will be summarized for all subjects included in the analysis. Continuous variables will be summarized using summary statistics (mean, standard deviation, median, range combined with 95% confidence interval calculations) and categorical variables will be summarized using counts and percentages.
In particular, the following tests according to the parameters type are going to be performed:

- Continuous parameters will be presented by the estimated value and calculation of 95% confidence intervals. In addition, the comparison will be by using the relevant Student's t-test.
- Categorical parameters will be analyzed by Fisher exact test/ chi-square tests (in case of low observed frequencies).

Tests will be two-sided in accordance to the hypothesis regarding the tested parameters, with a significance level of 0.05.

Sample Size

Up to thirty (30) patients are expected to complete the study.
The primary endpoint of the study will be to demonstrate that the Peregrine Endoscope will perform comparable to or better than a Standard 70° 4mm Endoscope, where a difference of 20% or more between visualization success rates will be considered to be statistically significant. Per protocol, a sub-group analysis of each of the different sinus cavities (i.e., Frontal, Maxillary and Sphenoid) will be used for power calculation.
In order to maintain minimal Power 80% and Type I (=α) error of 5% to detect minimal differences of ±20%, a sample size of 7 samples is needed per sinus cavity. This number does not include an estimated 20-30% drop-out rate due to technical reasons unrelated to the device. Therefore, a sample size of 10 samples per each sinus cavity, and a total of 30 samples for all sinuses (total of up to 30 patients), will be recruited to the study.

8 RISK ANALYSIS

Risk analysis for the Sinusway device has been conducted as part of FDA 510k submission (K162916). The Risk analysis was revised following the modification applied to the Peregrine endoscope. This risk analysis is applicable to the proposed clinical investigation. The potential risks described below will be explained to the subject in the informed consent process. Risk and Benefits summary of the investigational device will be presented in the Investigator's brochure.

8.1 Potential risks – (Peregrine):

Endoscopy is a minimally invasive, diagnostic medical procedure (4). Overall, nasal endoscopy is a safe and low risk procedure. Occasionally, gagging, nosebleeds or coughing may occur as the endoscope is threaded through a nostril (5). Mucosal trauma and bleeding may rarely occur, particularly in susceptible patients with increased risk of bleeding, such as those receiving aspirin or other anticoagulant medications (i.e. Plavix®, Coumadin®, etc.). In addition, although not related to the endoscopic devices, adverse reactions to the topical decongestants or anesthetic provided prior to the procedure may occur prompting verification of patients' allergies prior to application

8.2 Definitions of Adverse Device Events and Adverse Events

Adverse Device Effect (ADE)

- An "Adverse Device Effect" is an adverse event related to the use of an investigational medical device.
- This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the installation, the operation, or any malfunction of the investigational medical device.
- This includes any event that is a result of a use error or intentional misuse.
- "Adverse Events" are defined as any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational medical device.
- This includes events related to the investigational device.
- This includes events related to the procedures involved (any procedure in the clinical investigation plan).
- For users or other persons this is restricted to events related to the investigational medical device.
- All Adverse device effects must be recorded in the CRF. A description of the event, including the start date, resolution date, action taken, and the outcome should be provided.

All adverse events will be graded for severity as follows:

Grade	Degree	Description
1	**Mild**	Symptom(s) barely noticeable to patient or does not make patient uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptom(s) but may be given because of personality of patient.
2	**Moderate**	Symptom(s) of a sufficient severity to make patient uncomfortable; performance of daily activity is influenced; patient is able to continue in study; treatment for symptom(s) may be needed.
3	**Severe**	Cause severe discomfort; symptoms cause incapacitation or significant impact on patient's daily life; severity may cause cessation of treatment with study device; treatment for symptom(s) may be given and/or patient hospitalized.
4	**Life-threatening**	May result in death if not promptly treated and reversed.
5	**Fatal**	Results in death

Relationship -whether or not the test procedure/device caused the adverse event

Degree	Description
Definitely	There is evidence of exposure to the test procedure/device , the AE is most likely to be explained by the test procedure / device than by another cause; the challenge is positive; rechallenge (if feasible) is positive; the AE shows a pattern consistent with previous knowledge of the test procedure / device.
Probably	There is evidence of exposure to the test procedure / device; the temporal sequence of the AE onset relative to the test procedure / device is reasonable; the AE is more likely explained by the test procedure / device than by another cause.
Possibly	There is evidence of exposure to the test procedure / device; the temporal sequence of the AE relative to the test procedure / device is reasonable; the AE could have been due to another equally likely cause;
Probably not	There is evidence of exposure to the test procedure / device; there is another more likely cause of the AE
Definitely not	The patient did not receive the test procedure / device; or temporal sequence of the AE onset relative to test procedure / device is not reasonable; or there is another obvious cause of the AE.

Action taken - whether or not the adverse event caused the subject to be discontinued from the study.

Clinical Outcome – whether the adverse event was resolved or ongoing.

All adverse events, including a worsening of physical examination findings, in comparison with baseline values, must be followed until the event resolves, the condition stabilizes, the event is otherwise explained, or the patient is lost to follow-up.

8.3 Definitions of Serious Adverse Device Effects and device deficiencies

Serious Adverse Device Effect (SADE)

A "Serious Adverse Device Effect" is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Serious Adverse Event (SAE)

A "Serious Adverse Event" is an adverse event that:

a) led to a death (Note: In the event of subject death during the conduct of the study, efforts should be made to perform an autopsy.)

b) led to a serious deterioration in health that either:

   1) resulted in a life-threatening illness or injury, or

   2) resulted in a permanent impairment of a body structure or a body function, or

   3) required in-patient hospitalization or prolongation of existing hospitalization, or

   4) resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function

c) led to fetal distress, fetal death or a congenital abnormality or birth defect.
   - This includes device deficiencies that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. These are handled under the SAE reporting system.
   - A planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered to be a serious adverse event.

8.4 Unanticipated Serious Adverse Device Effect (USADE)

Serious adverse device effect which by its nature, incidence severity or outcome has not been identified in the current version of the risk analysis report.

Anticipated: an effect which by its nature, incidence, severity or outcome has been previously identified in the literature. For example minor bleeding.

Please note: All procedures carry some risk but ENT endoscopy is very safe. Minor complications are uncommon and major complications are very rare.

8.5 Adverse Effects and Precautions

The subjects will be counseled concerning what to expect during the procedure and the importance of communicating any problems to the investigator.

8.6 Adverse Event Reporting

It is the responsibility of the investigator to document all treatment related and device related Adverse Events (ADE's), which occur during the course of the study. All ADEs will be recorded on the adverse events page of the CRF. Severity and relationship to study device will be assigned by the investigator as described in the section above. ADEs will be recorded after the subject has been admitted to the clinic Visit-2.

Any SAE, whether deemed device-related or not, must be reported to the site Ethics Committee and to the sponsor as soon as possible after the investigator has become aware of its occurrence even if not all the information is available at the time of initial contact.

The investigator must complete a SAE Form, and send it to the Sponsor within 24 hours of becoming aware of the event. Accompanying documentation, such as copies of hospital case reports, autopsy report, and other documents when applicable, should be sent as soon as they are available.

The site's Ethics Committee must also be duly notified and dealt with, according to the Hospital and FDA/Ministry of Health regulations. Subjects who have had a SAE must be followed clinically until all parameters (including laboratory) have either returned to normal or are stabilized.

9 DATA MANAGEMENT

Data from each subject will be recorded in source data and transmitted to case report forms (CRFs) supplied by the Sponsor. The data will be inserted manually and quality check for errors and omissions will be performed to ensure the accuracy of the entered data.

The source data should be completed during the study by qualified personnel. All data must be filled out using ball pens (not pencils), accurately and promptly following each relevant step of the study. The CRF should be completed in full, i.e., no fields should be left blank once the subject has completed the study. CRFs entries corrections must be made only by lining out (single line) incorrect data and writing in the revisions. All corrections must be initialed and dated by the individual performing/recording the correction. If the reason for the change is not obvious, an explanation for the change should be recorded and attached to the CRF. Blacking out or using correction fluid or an eraser is not allowed to correct or eliminate data. The investigator must review the CRFs for completeness and accuracy and must sign/date the forms where indicated.

The investigator will retain originals of CRFs, subject consent forms, and study data as permanent records for a period of 2 years or until the data is no longer required for regulatory purposes (the longest between these two).

Electronic CRFs may be used in this study. The electronic data capture (EDC) program complies with 21 CFR part 11.

10 MONITORING PLAN

Clinical Monitoring for this study will be managed by 3NT Medical. The Clinical Monitor is qualified by training and experience to oversee the conduct of this study. The Clinical Monitor's responsibilities include maintaining regular contact with each investigational site through telephone/email contact and on-site visits, to ensure that:

- The trial is conducted according to FDA, ICH-GCP and EN ISO 14155:2011 requirements;
- The Investigational Plan is followed;
- Complete, timely, and accurate data are submitted;
- Problems with inconsistent or incomplete data are addressed;
- Complications and unanticipated adverse effects are reported to the Sponsor and the IRB;
- The site facilities will be monitored to stay adequate to meet the requirements of the study.

The Clinical Monitor will initiate the Study during an on-site visit and will continue to perform on-site monitoring visits as frequently as deemed necessary. The first monitoring visit will usually be made as soon as possible after enrollment has been initiated. At this visit and all monitoring visits, the Clinical Monitor will compare the data entered onto the CRFs with the hospital or clinical records (source documents). Source documentation must be available to substantiate proper informed consent procedures, adherence to protocol procedures, adequate reporting and follow-up of AEs, and device procedure information. Findings from the review of CRFs and source documents during a monitoring visit will be discussed with the PI. Completed paper CRFs will be reviewed prior to data closure at each visit. The dates of the monitoring visits will be recorded in a Log to be kept at the clinical site. During monitoring visits, the Sponsor expects that the study coordinator and the PI will be available, the source documentation will be available, and a suitable environment will be provided for review of Study related documents.

Monitoring procedures will follow the Sponsor SOPs.

11 INVESTIGATOR RESPONSIBILITIES

All principal investigators will be required to sign an Investigator Agreement

12 AMENDMENTS TO THE PROTOCOL

No alterations or changes to this protocol will be permitted. However, should there be question or consideration of deviation from the protocol, clarification and approval must be sought from the sponsor.

Protocol modifications must be confirmed in writing prior to implementation.

13 DEVIATION FROM THE STUDY PLAN

All major protocol amendments must be approved by the EC/IRB prior to implementation.

No protocol amendments should be adopted without prior written approval from the IRB except **in the following cases:**

- In order to eliminate immediate hazard to the subjects
- Changes involving only logistical or administrative aspects of the trial.

The investigator should document and explain any deviation from the approved protocol and to file waivers received from the sponsor, if applicable. The reasons for it, and, if appropriate, the proposed protocol amendments should be submitted to:

1. The Sponsor for agreement

2. The EC/IRB

Any subject treated in a manner that deviates from the protocol, or who is admitted into the study but is not eligible according to the protocol, may be ineligible for analysis and thereby compromises the study.

14 DEVICE ACCOUNTABILITY

3NT Medical will provide the study site with Peregrine devices and imaging/recording system for the duration of the study. The systems will be marked “for investigational use” and the investigator is responsible for storing the systems in a secure place to avoid unauthorized use.

Immediately upon completion of the study all systems and unused items will be returned to 3NT Medical.

15 VULNERABLE POPULATION

No vulnerable population will be included in this study.

16 SUBJECT CONFIDENTIALITY

Subject confidentiality will be maintained throughout this study, including all publications. Data collected and entered into the CRFs are the property of the study sponsor. Representatives from the study sponsor or authorized sponsor representatives, the Institutional Review Board (IRB), Ethics Committee, FDA may receive copies of the study records and may review medical records related to the study.

17 SUBJECT WITHDRAWAL OR DISCONTINUATION

Any patient will be informed of his right to withdraw from the study at any time and for any reason.

The Investigator or Sponsor may withdraw a patient from the study at any time if he considers that remaining in the study compromises the patient's health or the patient is not sufficiently cooperative.

The reasons for any patient withdrawal will be recorded on the study completion form of the CRF.

The investigator will inform the Sponsor in writing of the subject's early withdrawal for any reason.

If withdrawal is caused by an adverse event that the investigator considers may be related to the device, it will be reported to the EC/IRB and to the Sponsor.

18 SUSPENSION OR PREMATURE TERMINATION OF THE STUDY

The Sponsor reserves the right to discontinue the study at any time for any reason based on (but not exclusively) the following criteria:

- Technical problems in the device.
- Unanticipated Serious adverse device effect (USADE)
- The Principal Investigator's or the Ethics Committee recommendation
- Poor performance or compliance of the clinical site
- Company considerations

In case of premature termination of the study, the Ethics Committee will be duly informed according to the local regulations.

19 PUBLICATION POLICY

Any presentation/publication of complete or partial study data by the Investigators or any other party is stipulated by written authorization from the sponsor.

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