3NTMEDICAL
Access. See. Treat.

Title of the study: Safety and Effectiveness Evaluation of the Sinusway™ Device for Endoscopy of the Nasal Cavity and Paranasal Sinuses in Conjunction with Sinus Balloon Dilation

NCT No. : NCT03390257

Date of document: July 3rd, 2017

3NTMEDICAL
Access. See. Treat.

Clinical Protocol

Version Date	**July 3rd, 2017**
Amendment No.	**1**
Protocol Number	**SD-001**
Protocol Title	**Safety and Effectiveness Evaluation of the Sinusway™ Device for Endoscopy of the Nasal Cavity and Paranasal Sinuses in Conjunction with Sinus Balloon Dilation**

Approvals:

Site	**Sponsor**
_____	_____
Principal Investigator Date	Hadas Weiss Date
Signature	CT & RA Manager
	3NT MEDICAL

3NTMEDICAL
Access. See. Treat.

A Feasibility study to Evaluate the Safety and Initial Effectiveness of the Sinusway™ Device for Endoscopy of the Nasal Cavity and Paranasal Sinuses in Conjunction with Sinus Balloon Dilation

The Indications for Use claim for this system is –

The 3NT 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: **SD-001**

Date: **July 3, 2017**

3NT Medical

22 Hamelacha St., POB 11384,

Rosh Ha'ayin, 4809169

Israel

Table of Content

1 LIST OF ABBREVIATIONS

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

2 SYNOPSIS

Protocol Number	SD-001
Protocol Title	Safety and Effectiveness Evaluation of the Sinusway™ Device for Endoscopy of the Nasal Cavity and Paranasal Sinuses in Conjunction with Sinus Balloon Dilation
Participating Countries	USA
Clinical Phase	Open, multi - center, prospective, feasibility study
Investigational Study Device	Sinusway™, a flexible, steerable endoscope, by 3NT Medical Ltd.
Study Procedures	Up to 15 Patients scheduled for sinus balloon dilation will be examined with Sinusway™ before and as part of balloon sinus dilation in the operation room (OR) or office setting (Office). The patients will attend the following: 1. Visit 1: Screening and Enrollment, as part of pre-operative visit 2. Visit 2: Sinusway evaluation at the time of the procedure
Study Population	15 adult patients, male or female, scheduled for Sinus Balloon Dilation.
Study Purpose	To assess the safety and initial performance of Sinusway™ in patients in terms of access and visualization of the nasal anatomy and paranasal sinuses, usability (alone and in conjunction with balloon dilation instruments), visualization quality, and irrigation.
Study Endpoints	**Primary – Safety Endpoints:** • Device related adverse events **Secondary – Performance Endpoints:** • To evaluate the ability to access and visualize the nasal anatomy including the maxillary, frontal, and sphenoid sinuses. • To evaluate usability by filling a user questionnaire • To evaluate irrigation of the nasal anatomy
Inclusion/ Exclusion Criteria	**Inclusion Criteria:** 1. Male or female patient indicated for balloon sinus dilation procedure by the ENT specialist 2. Patient age: adult (>18 years old) 3. Patients in general good health in the opinion of the investigator as determined by medical history and physical examination

	4. 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. Known history of any significant medical disorder, which in the investigator's judgment contraindicates the patient's participation 2. Patients with known current or previous bleeding disorder receiving anticoagulants (e.g., chronic Coumadin treatment)
Study Duration	Per Patient: between 1 day and 30 days, depending on the interval between pre-operative visit (inclusion) and day of procedure. Total 10 months to recruit and treat 15 patients.
Statistical Analysis Plan	NA

3 BACKGROUND

3.1 Nasal Endoscopy

The paranasal sinuses are 4 pairs of air-filled bony spaces that surround the nasal cavity and are lined with mucous membrane densely covered with cilia that facilitates mucociliary clearance and drainage into the nasal cavity. Infection of sinuses, or rhinosinusitis (RS), is caused when mucociliary functionality is compromised and/or the sinus ostia is compromised causing the sinuses to become congested and eventually blocked. RS is a severely debilitating quality of life condition, which is characterized by throbbing headaches and facial pressure, purulent nasal discharge, and nasal obstruction. Chronic rhinosinusitis (CRS) is a chronic disease that involves long-term inflammation of the nasal and paranasal sinus mucosa with a minimum duration of 12 weeks. CRS causes not only physical suffering, but also impacts psychological wellbeing and daily functioning. CRS is an extremely common condition, affecting 29.2 million (14.2%) US adults.

Nasal endoscopy is the most important diagnostic tool currently available to otolaryngologists to diagnose sino-nasal disorders [1]. Current endoscopes perform well at allowing otolaryngologists to evaluate the nasal cavity. When anatomy is favorable, endoscopes also visualize regions externally adjacent to the sinus ostia, but do not allow visualization, culture, or lavage of the sinus cavity without extensive prior surgical opening.

The endpoints of nasal endoscopy include the ability to diagnose the patient's condition and obtain a nasal culture that has some correlation with the sinus cavity contents [2]. The limitations include the inability to steer into or around narrow anatomy, to obtain an intra-sinus culture, and to visualize the sinus cavity.

A CT scan is required when diagnosing chronic sino-nasal disorders like CRS. A CT scan provides information as to whether the sinus is clear or opacified, but is often limited in providing information as to what is opacifying the sinus cavity [3]. Most importantly, CT scan is associated with radiation exposure harmful to the patient and should be avoided if possible.

Sinusway, a flexible, steerable endoscope, overcomes current technological limitations by providing sinus visualization, and irrigation. Sinusway does not pose any risk additional to the minor risks already associated with current sino-nasal endoscopy; furthermore, the risks of bleeding, pain are reduced due to the flexibility and small profile of the device which minimizes contact with the anatomy. The risk of infection is eliminated as the intra-nasal component of the device is a one-time single use disposable and does not require re-sterilization between patients.

3.2 Functional Endoscopic Sinus Surgery (FESS) and Balloon Sinus Dilation (BSD)

The objective of FESS is to open the natural pathways to the sinuses. Once an improved drainage system is achieved, the diseased sinus mucosa has an opportunity to return to normal. FESS involves the insertion of endoscope into the nose for a direct visual examination of the openings into the sinuses. Diseased or obstructive sinus tissue may be removed resulting in improved natural sinus drainage.

There are several sinus surgery options that can be performed in a hospital operating room or doctor's office. Balloon sinus dilation (BSD) is a minimally invasive surgery that can be performed in both settings. A small balloon is inserted into the nose; once in the right spot, it is inflated to open and drain blocked sinus pathways. The goal of balloon sinus surgery is to unblock sinus pathways and improve symptoms, reduce infections, minimize sinus headaches and restore quality of life. When performed in the doctor's office, it offers faster recovery times and may allow eligible patients to have a lower out-of-pocket cost.

3.3 The Sinusway Device

Sinusway, developed by 3NT Medical, is a single-use disposable handheld endoscope 2.3mm in diameter that provides a means to visualize the internal cavities of the ear, airways, nose and sinus cavities during diagnostic and therapeutic endoscope procedures.

An ENT specialist may use the device in an operating room (OR) or an office setting, for visualization and for irrigation at anatomic landmarks, including the sinuses cavities, currently inaccessible by existing endoscopes without significant surgical resection of bone and tissue.

3NT endoscopy system (See figure 1 below) includes:

1. A Multi-use handle accessory (re-processible and auto-clavable) – engages the single-use endoscope component and allows the user to mechanically control its articulation through dedicated levers. (see Figure 1, Reusable Handle)

2. A Single-use flexible endoscope (provided sterile) – includes a distal tip CMOS imager and an integrated working channel which allows irrigation through a single channel. It is the only part that comes in contact with the patient and is disposed of at the end of the procedure. (see Figure 2, Disposable Endoscope).

3. A Camera control unit (CCU) – includes a video processor and a white LED light source. The CCU includes an attachment cable which connects to the single-use endoscope, receives video images from the endoscope, and delivers LED light to the endoscope.

Figure 1 - Reusable Handle

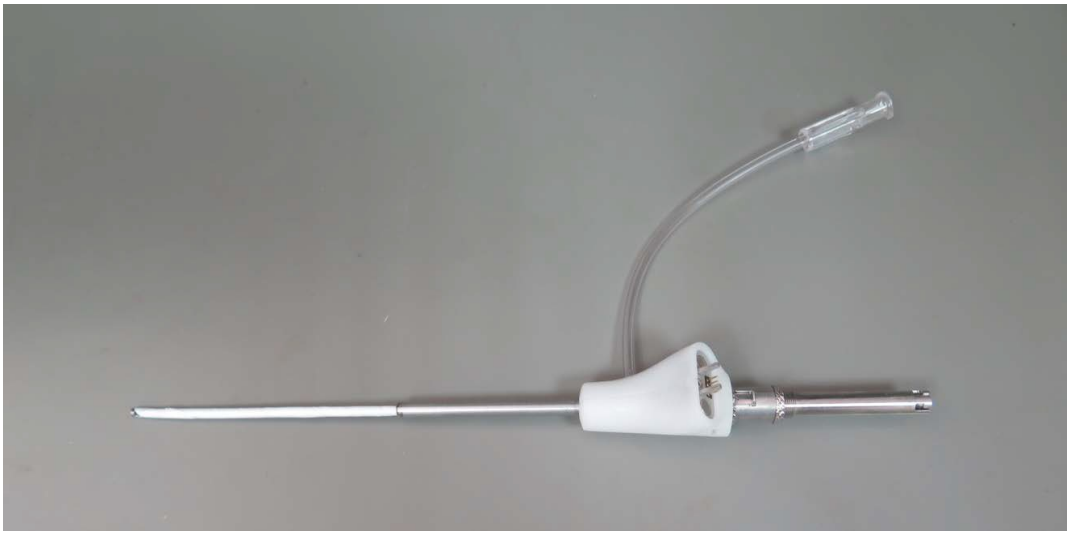

Figure 2 - Disposable Endoscope

The Sinusway endoscope contains an articulation mechanism that supports angulation of 125˚ and advancement of the insertion tube over the angulated section and beyond it, effectively keeping the angulated section stationary with respect to the anatomy (See Figure 3).

Figure 3 Angulation and advancement of the flexible endoscope

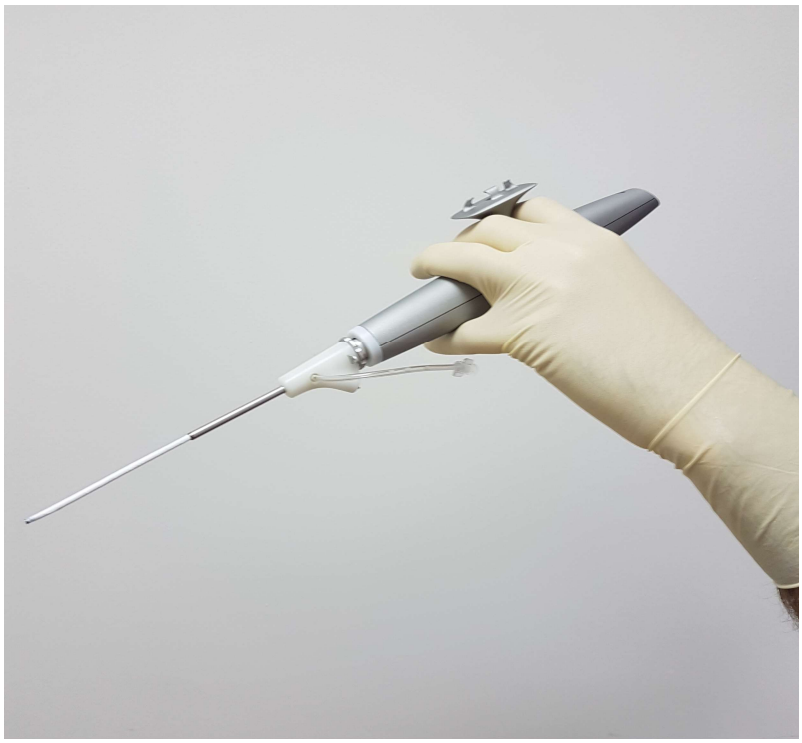

Figure 4 Assembled Endoscope

When used in conjunction with a commercially available balloon dilation device, the Sinusway may facilitate minimally invasive endoscopic sinus surgery with less post-operative nasal bleeding, faster recovery time, shorter duration of prescription medication use and short term symptom improvement than traditional FESS. [4]

3.4 Clinical Experience with Sinusway

3NT Medical is currently conducting a clinical study in Belgium and Israel to assess the safety and initial performance of Sinusway. The study evaluates the ability of the endoscope to access and visualize the nasal anatomy and paranasal sinuses, the endoscope usability, visualization quality, and irrigation in patients undergoing FESS surgery.
The Sinusway endoscope was evaluated during eleven (11) functional endoscopic sinus surgeries (FESS) occurring in the operating room under general anesthesia. Six (6) cases were performed in two sites in Israel: Assuta M.C.(3) and Rabin M.C.(3). Five cases were performed at the University of Ghent, Belgium. Mean Subject age was 44.3 Years [23-60 yrs], 6 males, 5 females. No major technical issues were observed during the operation of the system. No adverse event reported. Device operation and physician feedback were satisfactory.

4 OBJECTIVES

The objective of this study is to assess the safety and initial performance of Sinusway in patients in terms of access and visualization of the nasal anatomy and paranasal sinuses, usability (alone and in conjunction with balloon dilation instruments), visualization quality, and irrigation.

For this study, up to 15 patients scheduled for sinus balloon dilation will be examined with Sinusway before and as part of balloon dilation in the operation room (OR) or office setting (Office). Additional endoscopes as available in the procedure room and as commonly used by the ENT specialist may be used.

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

1. Ability to access the nasal anatomy and paranasal sinuses: Ability to access and visualize anatomic landmarks, including the maxillary, frontal and sphenoid sinuses, will be recorded. Successful access will be confirmed by direct visualization and transillumination where applicable.

2. Usability evaluation

3. Irrigation evaluation
4. Nasal cavity and sinuses inflammation evaluation

5. Patient pain score and tolerability, when applicable

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 literature for Nasal Endoscopy (section 8).

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

Secondary - Performance

- To evaluate the ability to access and visualize the nasal anatomy including the maxillary, frontal, and sphenoid sinuses (according to physician discretion). This ability will be verified by observing anatomic landmarks and transillumination (as Done/Not Done/Failed).

- To evaluate usability and user satisfaction- by filling a usability questionnaire regarding the device, including assessment of visualization quality. Will be completed by the user

Other Measurement – Performance

- To evaluate irrigation of the nasal anatomy (as Done/Not Done, which sinus was irrigated)
- To evaluate nasal cavity inflammation and sinuses inflammation using Lund Mackay CT score and Lund Kennedy Endoscopic scoring
- Patient tolerability and Pain assessment will be recorded by a 0-10 scale (when applicable)

5 DESCRIPTION OF PATIENT POPULATION

5.1 Patient Selection

Patients indicated for balloon sinus dilation procedure by the ENT specialist.

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. Male or female patient indicated for balloon sinus dilation procedure by the ENT specialist
2. Patient age: adult (>18 years old)
3. Patients in general good health in the opinion of the investigator as determined by medical history and physical examination
4. 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. Known history of any significant medical disorder, which in the investigator's judgment contraindicates the patient's participation
2. Patients with known current or previous bleeding disorder receiving anticoagulants (e.g., chronic Coumadin treatment)

6 INVESTIGATION PLAN

6.1 Study Design

Type of Study

This is an open, multi-center, prospective, feasibility study in which the investigational device, the Sinusway, will be tested in a single group of adult patients, male or females.

The rationale behind this feasibility study is to show that access and visualization of the nasal anatomy and paranasal sinuses (Maxillary, Frontal and Sphenoid sinuses) in conjunction with Balloon Sinus Dilation in patients suffering from symptoms attributable to sinusitis is feasible in the office and operating room settings; This is an essential step in the development of a combined dilation and visualization system that will allow visualization, dilation and lavage of the sinuses via their natural ostia during an office visit, and minimize radiation exposure, antibiotic use, multiple office visits, and cost.

This study is proposed after completing a series of clinical cases, 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

No control groups and no randomization will be utilized in this study since its primary objectives are to obtain information on safety, tolerability and usability which may serve as a basis for modification (if required) and future controlled studies.

6.2 Study Procedures

Visits 1: Screening

- Screening will take place within 1 day-30 days before the procedure.
- Patients potentially qualifying for the study will be offered an Informed Consent to sign prior to further evaluation. Any patients not qualifying will be exited from the study as screening failures and will not be included in the safety/effectiveness analyses.

- The following screening assessments will be performed at pre-study for each patient:
  - Medical history (including concomitant medications)
  - Sino-Nasal outcome test (SNOT-20)
  - Vital signs (optional)
  - CT
  - Laboratory blood work within 6 months including Hematocrit, White Blood Cells , PT, PTT, INR, Creatinine and Glucose (optional, only if done prior to surgery)
  - Compliance with inclusion/exclusion criteria
  - Patients found eligible to participate in the study in the initial screening will be scheduled to undergo the Sinusway evaluation.

Visit 2: Procedure and Study Termination

- **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 may undergo BSD under local anesthesia, intravenous sedation and local anesthesia or under general anesthesia, at physician discretion.
  2. The Sinusway device will be prepared for use per its instructions for use.
  3. Evaluation of the patient with physician's typical rigid endoscope(s). Visualization of the sinuses (frontal, maxillary, sphenoid) will be recorded as performed/failed and an Image of the anatomic landmark will be taken.

4. Following the Evaluation with physician's typical rigid endoscope(s) the evaluation will be repeated using the Sinusway endoscope. Access to the sinuses (frontal, maxillary, sphenoid) will be recorded as performed/failed and an Image of the anatomic landmark will be taken. Nasal Cavity and sinuses inflammation score will be captured using the Lund Mackay CT and endoscopy score.
5. BSD procedure will be performed with either endoscope.
6. Irrigation of the nasal anatomy will be performed and recorded as Done/Not Done and which sinus was irrigated.
7. Following the BSD procedure, repeated evaluation of patient's sinuses and nasal cavity will be performed using the Sinusway endoscope
8. Usability assessment will be completed by physician.
9. If applicable, patient pain assessment using a 0-10 pain Scale and patient tolerability will be captured (Office procedures only)

- **After the procedure:**

- The patient will recover from the procedure per physician's common practice. Before patient's release, recording of AE, if any, will be performed. Patient will exit the study.

6.3 Methods and Timing for assessments

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

Table 1: Study visit schedule		
Study Activities	**Session I:** **Screening and Inclusion V-1**	**Session II:** **Procedure V-2** **Within 30 days post screening**
Informed Consent	x	
Demographic Data	x	
Medical History	x	
SNOT 20	x	
Concomitant medication	x	
Physical Examination	x	
Laboratory test (Optional as commonly done for BSD)	x	
Vital Signs (optional)	x	
Inclusion/exclusion criteria	x	
CT scan (as commonly done for BSD)	x	
Lund Mackay/Kennedy inflammation score	x	x
Endoscopy with Sinusway and Commercially Available Endoscope		x
Balloon sinus dilation Followed by Sinusway Endoscopy		x
User questionnaire		x
Patient tolerability and pain score		x
AEs/SAEs		x
Patient Exit		x

7 STATISTICAL CONSIDERATIONS AND SAMPLE SIZE

Statistical Considerations

No statistical analysis will be used as this is a feasibility safety study.

Sample Size

Up to Fifteen (15) patients are expected to complete the study at all sites

8 RISK ANALYSIS

Risk analysis for The Sinusway device has been conducted as part of FDA 510k submission (K162916). 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.

8.1 Potential risks – (Sinusway):

Endoscopy is a minimally invasive, diagnostic medical procedure. Overall, nasal endoscopy is a safe and low risk procedure. Nonetheless, potential complications such as mucosal trauma and bleeding may 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, adverse reactions to the topical decongestants or anesthetic provided prior to the procedure may occur.
Since the Sinusway endoscope will be used in conjunction with balloon sinus dilation, the following risks which are associated with BSD and/or endoscopic sinus surgery are presented.

Risk associated with Endoscopic Sinus Surgery

Surgeons performing routine endoscopic interventions are faced with minor complications in 5% and major complications in 0.5–1% [21]

- Infection- A patient with sinusitis is at risk of developing infection (abscesses, meningitis, etc.) Infection risk increases with the invasiveness of the intervention. The rate of intracranial infections where the intervention is maximized is 1.6% and the rate of infection-related mortality is 0.125%. It is comparable to the one of transcranial surgeries not involving the use of an endoscope [5,6,7]. The Risk of Infection following Sinusway use is mitigated since the Sinusway endoscope is a disposable intended for single use only.

- Bleeding- Bleeding may occur, particularly in susceptible patients with increased risk of bleeding, such as those receiving aspirin or other anticoagulant medications (i.e. Plavix, Coumadin, etc.) [20]. The rate of peri- or postoperative bleeding is around 2% altogether; transfusions were required in about 0.2% of cases [8,9].

- Nasomucosal injury- Nasomucosal injury may occur during transnasal endoscopy. Nasomucosal injury was assessed in 1569 patient that underwent unsedated transnasal esophagogastroduodenoscopy (EGD), at termination of the procedure. Normal mucosa was observed in 68% of cases, redness of mucosa was observed in 19% of cases, oozing hemorrhage was observed in 12% of cases and overt bleeding was observed in 2% of cases. The hemorrhage was self-limiting and no patient required nasopharyngeal treatment [10].
- CSF leakage - Small and isolated CSF fistulas, which are treated at once successfully, are considered as minor complication in sinus surgeries [11]. These particular incidents are not rare – in a survey, 25% of American otorhinolaryngologists had experienced at least one unexpected CSF fistula intraoperatively during endoscopic sinus surgeries within 5 years [12]. The rate of unexpected dura exposure is reported with a percentage of 0.2% [8]. The number of minimal, temporary and occult leakage of cerebrospinal fluid ceasing spontaneously without clinical relevance, is significantly higher [13]. Once a small cerebrospinal fluid leak is confirmed, references recommend conservative treatment to begin with [12, 14, 15, 16]. In a few cases lumbar drainage was solely carried out [17]. However, in case of a persisting leak encountered during routine sinus surgeries or e.g. after rhino-neurosurgical procedures, surgical treatment should be pursued even with small defects.
- Orbital hematoma - The incidence of orbital hematomas is around 0.1% in all procedures [18, 19]. Visual loss and blindness have been reported but are extremely rare. Another uncommon problem is damage to the muscles that move the eye, leading to double vision, which can be temporary or permanent. In certain circumstances, there may be a change in the function of the tear ducts causing excessive tearing. Since the eye is in close proximity to the sinuses, a major orbital complication or blindness could possibly occur even without surgery for patients with severe or refractory sinus infections.
- Voice changes - One of the functions of the sinuses is to affect resonance, therefore, there is a potential change in the voice after sinus surgery.
- Impaired sense of taste or smell - The sense of smell usually improves after the procedure because airflow is restored, although in sporadic cases it could worsen depending on the extent of swelling, infection, or allergy. This impairment is often temporary but can be prolonged.
- Nasal obstruction, dryness and pain - Although preventative measures are performed by the surgeon at the time of procedure, the cartilage may move after the surgery which may rarely lead to persistent blockage. Surgery typically improves airflow, but in some patients, it may not improve or rarely may worsen. Small scar bands may also occur in the nose and require removal by the surgeon at postoperative visits. Over-aggressive resection of the turbinate structures may leave some patients with the sensation of being overly dry or even cause chronic pain.
- Adverse reactions to the topical decongestants or anesthetic provided prior to the procedure may occur. Thus, before administering these topical medications, patients' allergies should be verified

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 implantation, 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.

Degree	Description
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.

Anticipated adverse events

Anticipated adverse device effects include Infection, Excessive Bleeding, Nasomucosal injury, CSF leakage, Orbital hematoma, Voice changes, Impaired sense of taste or smell, Nasal obstruction, dryness and pain and Adverse reactions to the topical decongestants or anesthetic provided prior to the procedure. Please refer to section 8.1 above

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).

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 Sinusway 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.

20 REFRENCES

1 Josef Shargorodsky, MD, MPH, et al.: What is the Role of Nasal Endoscopy in the Diagnosis of Chronic Rhinosinusitis? The Laryngoscope (2012), The American Laryngological Rhinological and Otological Society, Inc.

2 Michael S. Benninger, MD, et al.: Endoscopically Directed Middle Meatal Cultures versus Maxillary Sinus Taps in Acute Bacterial Maxillary Rhinosinusitis: A Meta-Analysis, Otolaryngology–Head and Neck Surgery (2006) 134, 3-9

3 Use of Diagnostic Imaging Studies and Associated Radiation Exposure for Patients Enrolled in Large Integrated Health Care Systems, 1996-2010, JAMA, June 13, 2012—Vol 307, No. 22

4 Jeffrey Cutler, M.D., Nadim Bikhazi, et al.: Standalone balloon dilation versus sinus surgery for chronic rhinosinusitis: A prospective, multicenter, randomized, controlled trial, Am J Rhinol Allergy 27, 2013, 416–422

5 Hosemann, W., & Draf, C. (2013). Danger points, complications and medico-legal aspects in endoscopic sinus surgery. GMS current topics in otorhinolaryngology, head and neck surgery, 12.

6 Kassam, A. B., Prevedello, D. M., Carrau, R. L., Snyderman, C. H., Thomas, A., Gardner, P., & Horowitz, M. B. (2011). Endoscopic endonasal skull base surgery: analysis of complications in the authors' initial 800 patients: a review. Journal of neurosurgery, 114(6), 1544-1568.

7 Kramer, A., Kohnen, W., Israel, S., Ryll, S., Hübner, N. O., Luckhaupt, H., & Hosemann, W. (2015). Principles of infection prevention and reprocessing in ENT endoscopy. GMS current topics in otorhinolaryngology, head and neck surgery, 14.

8 Dalziel, K., Stein, K., Round, A., Garside, R., & Royle, P. (2006). Endoscopic sinus surgery for the excision of nasal polyps: A systematic review of safety and effectiveness. American journal of rhinology, 20(5), 506-519.

9 Vleming, M., Middelweerd, R. J., & de Vries, N. (1992). Complications of endoscopic sinus surgery.Archives of Otolaryngology–Head & Neck Surgery,118(6), 617-623.

10 Mori, A., Ohashi, N., Maruyama, T., Ito, M., Miyawaki, T., & Okuno, M. (2008). A proposal for grading nasomucosal injury as a complication of transnasal endoscopy. Endoscopy, 40(S 02), E60-E60

11 Rombout, J., & de Vries, N. (2001). Complications in sinus surgery and new classification proposal.American journal of rhinology, 15(6), 363-370.

12 Platt, M. P., Shaye, D., & Parnes, S. M. (2007). Management of unexpected cerebrospinal fluid fistulae during endoscopic sinus surgery. American journal of rhinology, 21(5), 611-614.

13 Bachmann, G., Djenabi, U., Jungehülsing, M., Petereit, H., & Michel, O. (2002). Incidence of occult cerebrospinal fluid fistula during paranasal sinus surgery. Archives of Otolaryngology–Head & Neck Surgery, 128(11), 1299-1302.

14 Hegazy, H. M., Carrau, R. L., Snyderman, C. H., Kassam, A., & Zweig, J. (2000). Transnasal Endoscopic Repair of Cerebrospinal Fluid Rhinorrhea: A Meta-Analysis. The Laryngoscope,110(7), 1166-1172.

15 Casiano, R. R., & Jassir, D. (1999). Endoscopic cerebrospinal fluid rhinorrhea repair: is a lumbar drain necessary?. Otolaryngology--Head and Neck Surgery, 121(6), 745-750.

16 DelGaudio, J. M., & Ingley, A. P. (2010). Treatment of pneumocephalus after endoscopic sinus and microscopic skull base surgery. American journal of otolaryngology, 31(4), 226-230.

17 Warnecke, A., Averbeck, T., Wurster, U., Harmening, M., Lenarz, T., & Stöver, T. (2004). Diagnostic relevance of β2-Transferrin for the detection of cerebrospinal fluid fistulas. Archives of Otolaryngology–Head & Neck Surgery, 130(10), 1178-1184.

18 Bhatti, M. T., & Stankiewicz, J. A. (2003). Ophthalmic complications of endoscopic sinus surgery. Survey of ophthalmology, 48(4), 389-402.

19 Ramakrishnan, V. R., & Palmer, J. N. (2010). Prevention and management of orbital hematoma.Otolaryngologic Clinics of North America, 43(4), 789-800.

20 Soudry, E., & Nayak, J. V. (2015, February 17). Nasal Endoscopy. Retrieved August 21, 2016, from http://care.american-rhinologic.org/nasal_endoscopy

21 W. Hosemann, C. Draf, . (2013). Danger points, complications and medico-legal aspects in endoscopic sinus surgery, Head and Neck Surgery, Vol. 12

21 APPENDICES

Appendix-A: Informed Consent

Appendix-B: Case Report Forms