INVESTIGATIONAL PLAN FOR CONTINUED EVALUATION OF THE PRECEPTIS MEDICAL INC. TYMPANOSTOMY EAR TUBE INTRODUCER

A Non-Significant Risk Investigation

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INVESTIGATIONAL PLAN SUMMARY

1.0 BACKGROUND

1.1 Device Name

The Preceptis Tympanostomy Tube Introducer (TTI)

1.2 Device Description

The tympanostomy tube introducer (TTI) is a disposable surgical tool designed to deliver a tympanostomy tube ("ear tube") into the tympanic membrane of patients during a tympanostomy tube placement procedure.

More than 1,000,000 ear tubes are inserted annually in the US, making it one of the most common surgical procedures performed in children. Most ear tubes are inserted by ENT surgeons with the patient under either local anesthesia (usually adults) or general anesthesia (usually children).

Preceptis Medical, Inc. has developed the TTI surgical device to reduce trauma, pain, and risk to the patient while reducing the overall surgical procedure time. The TTI device integrates the multiple surgical instruments necessary for current surgical procedure into a single, one-action device. The TTI device creates an incision in the tympanic membrane ("ear drum") and inserts a tympanostomy tube with the push of a lever, all while providing suction and fluid extraction capability. Thus, the TTI device allows placement of a tympanostomy tube with a single pass down the ear canal. The ear tube used with the TTI device is a standard, commercially available tympanostomy tube.

1.3 Pre-Clinical Testing

The TTI device has successfully undergone bench and cadaver tympanic membrane tests.

1.4 Summary of Previous Clinical Results

As of 30 August 2013, 60 patients had been enrolled under "Investigational Plan for Evaluation of the Preceptis Medical, Inc. Tympanostomy Tube Introducer (TTI)" at the University of Minnesota, Amplatz Children's Hospital and Minneapolis Children's Hospital.

Per procedural outcomes and feedback from the ENT surgeons, the TTI is reducing surgical trauma for the patient as designed. All tubes have been successfully delivered across the tympanic membrane. Safety is being evaluated by an independent ENT reviewer, and there have been no safety issues. There have been

three AE's reported in the study: one case of otorrhea in an adult patient at the initial follow-up visit, a tube extrusion in the same adult patient at the subsequent follow-up visit, and a tube extrusion at the follow-up visit in a child. None of these AE's were unanticipated, and all were non-serious. The tympanostomy procedures have taken place in the operating room, the office, and the sedation unit.

1.5 Clinical and Regulatory Background

Per 21 CFR 874.4420, the ear tube introducer is defined as a myringotomy tube inserter and is classified by the US Food and Drug Administration as Class I (general controls). The device is exempt from the premarket notification procedures (i.e., 510(k) clearance process) in subpart E of 21 CFR part 807.

1.6 Indications for Use and Intended Use

The TTI device is indicated for patients undergoing a tympanostomy tube procedure. The TTI device is intended to deliver a tympanostomy tube through the tympanic membrane of a patient during a tympanostomy procedure.

2.0 STUDY OBJECTIVES

The objective of this study is to evaluate the safety and performance of the TTI device for the placement of ear tubes in patients undergoing a tympanostomy tube placement procedure.

3.0 STUDY DESIGN OVERVIEW AND DURATION

The trial will be a multi-site, prospective, treatment only study of the Preceptis ear tube introducer . Patients will already have a scheduled tympanostomy procedure.

Enrollment in the study at each site will begin after receipt of Institutional Review Board (IRB) approval. Patients will be considered enrolled at the time the informed consent document is signed. A maximum of two hundred fifty (250) subjects will be included in the study at up to 5 sites.

Estimated study start date:	*September 2013 (but upon IRB approval)*
Estimated enrollment completion date:	*May 2014*
Estimated study completion:	*Dec 2015*

4.0 STUDY ENDPOINTS

4.1 Safety Endpoint

The rate of overall AEs, and for each specific type of event, will be estimated.

4.2 Efficacy Endpoint

Efficacy evaluation will consist of determining whether the TTI device successfully delivers the tympanostomy tube across the tympanic membrane and whether the tube is still in place at the initial follow-up visit and at follow-up visits at 6-month intervals until the tube is extruded.

5.0 STATISTICAL METHODS AND DATA ANALYSIS

5.1 Data Analysis

Data from this feasibility study will be analyzed on an As-Treated basis using a common closing date. Standard summary statistics will be calculated for all study outcome variables. Categorical data will be summarized in frequency distributions. Detailed summaries of all adverse events will be provided. The rate of adverse events and the delivery success rate will be calculated, along with corresponding 95% exact confidence intervals. These data will be compared to published AE rates and/or investigator experience with standard tympanostomy procedures. The proportions of successfully delivered tubes will be calculated, along with the corresponding 95% exact confidence intervals.

Study success will be determined based on a qualitative clinical analysis of all data.

5.2 Enrollment

5.2.1 A patient will be considered enrolled at the time the informed consent document is signed. Inclusion and exclusion evaluation will not require baseline testing and will thus be evaluated prior to signing the consent**.**

5.2.2 Enrollment may begin when the following criteria are met:

- IRB approval of the study protocol and informed consent document.
- Signed Investigator Agreement-Clinical Study Agreement.
- Completion of bench training regarding use of the ear tube introducer. This is required for each surgeon prior to performing their first case.
- Investigational site personnel training on the study protocol.
- Inclusion-exclusion criteria are met for each patient.

6.0 SAMPLE SIZE

Up to 250 enrolled patients will be included in this trial. Enrollment is expected to be approximately 95% children and 5% adults and approximately evenly divided between gender. A total sample size of 250 subjects will provide sufficiently precise estimates of adverse event and delivery success rates to assess the feasibility of the Preceptis TTI and for publication purposes. The results from this study may be used to support the design and initiation of a larger study of this device.

7.0 PATIENT POPULATION

7.1 Selection Criteria

Patients considered for this trial will meet all of the inclusion criteria in section 7.2 below. However, if they meet ***any*** of the exclusion criteria in section 7.3, they will not be eligible to participate in the trial.

7.2 Inclusion Criteria

Patients must meet ***all*** of the following:

1. Scheduled to undergo tympanostomy tube insertion.
2. At least 6 months old.
3. Subject is able and willing to comply with follow-up requirements.
4. Signed Informed Consent, Parental Consent Form, or Child Assent Form as applicable.

7.3 Exclusion Criteria

Patients will be excluded should they meet ***any*** of the following:

1. Any condition that in the opinion of the investigator may place the subject at greater risk (e.g., pregnancy)
2. Significantly atrophic tympanic membrane.
3. Significantly atelectatic tympanic membrane. For example, the tympanic membrane is in contact with the promontory of the cochlea.
4. Anatomy precludes sufficient visualization and access to the tympanic membrane.

8.0 SURGICAL PROCEDURE

The tympanostomy procedure will be identical to a standard tympanostomy procedure except for using the TTI device to make the myringotomy incision and place the tube rather than using standard, manual surgical instruments. Accordingly, the risks for this study are not expected to be any different than those associated with standard tympanostomy procedures. The tympanostomy procedures will take place in the operating room, the pediatric sedation unit or the office.

8.1 Anesthesia Protocol

Anesthesia for surgical treatment of otitis media ranges from topical anesthesia to sedation to general anesthesia. In a sedation unit or operating room, patients can receive sedation to general anesthesia. In infant to young pediatric populations, tympanostomy tube insertion is commonly done in an operating room with a patient under general anesthesia or deep sedation. In cooperative children and adult populations, tympanostomy tube placement is typically performed in a physician's office using topical anesthesia and/or sedation if available.

Anesthesia and patient monitoring will be consistent with what is currently done in an office, sedation unit, or operating room for tympanostomy tube placement surgery. Patients having tympanostomy tube surgery in a physician's office will receive topical

anesthesia on the ear drum. Patients having surgery in the sedation unit or operating room will receive nitrous oxide, sedation, or sevoflurane, depending on the anesthetic requirement of the patient.

9.0 CONSENT

Patients may be adults or children over the age of 6 months. As such, a standard Informed Consent form will be used for patients 18 years old and above. A Parental Consent form will be used for children who are 17 years old and younger. A Child Assent form will be used for children 8-17 years of age (age range may be dependent on the site). Prior to undergoing enrollment, the study will be explained to the patient and/or parents by the investigator and a consent form will be provided in the patient's (or parent's) native language. The consent forms must be approved by the IRB. All patients (or parents) will sign a consent form prior to enrollment.

Additionally, PHI created or received for the purposes of this study is protected under the federal regulation known as HIPAA. Patients will be required to sign a HIPAA form authorizing the principal investigator, research staff, and the sponsor access to their individual health information. Some sites may incorporate the HIPAA form within the informed consent.

The Consent forms are located in **Attachment A**.

10.0 STUDY PROCEDURES

10.1 Summary of Study Procedures

The primary investigators are responsible for the quality of all data submitted to the Sponsor. Documentation of patient eligibility, procedural experience, follow-up visit, adverse events, protocol deviations, and withdrawal will be reported on the case report forms (**Attachment B**). For purposes of scheduling follow-up visits, time zero is the date of surgery. Enrolled patients will undergo evaluation at the time of procedure, and at a follow-up visit 3-10 weeks days post-surgery and every 6 months (+/- 30 days) thereafter until the tube has extruded. Adverse events will be reported for each patient until their enrollment in the study is terminated.

CRF's	Type of Form	Timing
#1	Enrollment	Prior to surgery
#2	Procedure	Time of surgery
#3	Follow-up	3-10 weeks post-surgery and at 6-month intervals
#4	AE	As applicable
#5	Protocol Deviation	As applicable
#6	Patient Withdrawal	As applicable

10.1.1 Baseline Visit

Patients who are undergoing a tympanostomy tube procedure and meet all study inclusion criteria and none of the exclusion criteria will be approached for participation in the study by the PI or co-PI. If the patient agrees to participate, an informed consent will be collected. There are no further baseline tests required for the study.

10.1.2 Surgical Visit

Subjects who sign the informed consent form will proceed to the surgical visit. The type of anesthesia, total tympanostomy procedure time and adverse events will be documented.

10.1.3 Follow-up Visit

Subjects will return to the clinic between 3-10 weeks post-surgery and then at 6-month intervals (+/- 30 days) until the tube is extruded (standard of care). At these visits, the physician will assess the subject to determine if the tube is still in place and will document any adverse events. If standard of care at that institution, an audiogram will be performed post-surgically, and the ENT surgeon will provide commentary on the comparison of the pre and post-surgical audiograms for any evidence of hearing loss.

10.2 Study Termination

The safety and efficacy phases for each patient will begin at the implant procedure and end when their tympanostomy tube has extruded and enrollment in the study has been completed. After the last patient enrolled has completed their last follow-up visit, the study will be terminated. Once monitoring has been completed, the database will be frozen and a clinical report will be prepared and submitted to the IRB.

10.3 Stopping Rules/Safety Monitoring

The sponsor will appoint an independent ENT physician to review 100% of unanticipated adverse device effects. If any perceived safety issues arise, the trial may be suspended, and safety data will be analyzed. Additionally, the independent ENT will review all safety results at each interval of 20 patients whose surgery used the TTI. If any perceived safety issues arise per this review, the trial may be suspended, and safety data will be analyzed. If the Sponsor, the PI, and the independent reviewer agree that the study is safe to continue, the study may be re-started.

11.0 ADVERSE EVENTS

11.1 Reporting Criteria

Adverse events are reported as they occur during the course of the study, with the starting point being anesthetic administration during the tympanostomy procedure All adverse events, including the date, outcome management, and assessed relationship

of the event to the study device, must be recorded on the appropriate case report form. Adverse events may be anticipated or unanticipated.

Device related events are defined as follows: events that are likely related to the ear tube introducer as it relates to the act of placing the tympanostomy tube in the tympanic membrane and cause an adverse event. They result from a malfunction (operation not according to design specification) of the TTI or from interaction between the TTI and the patient.

11.2 Anticipated Adverse Events

Anticipated adverse events include those that are expected to occur in this study because they are typically associated with tympanostomy tube procedures. Conditions existing at the time of enrollment should not be reported as adverse events. Anticipated adverse events may be non-serious or serious.

Serious Adverse Events are defined as those which require an in-patient hospitalization ($\geq$ 24 hours), prolonged hospitalization, resulted in permanent hearing loss, resulted in death or required medical and surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or body function.

Adverse events, which resolve and recur, should be reported as separate events. Anticipated adverse events are defined in Attachment C.

11.3 Unanticipated Adverse Events

Unanticipated adverse events are events that are not considered anticipated, as defined in the previous section.

There are additional reporting requirements for the subset of unanticipated adverse events which are likely device related (UADE). Any adverse event that is unanticipated and likely device-related must be reported as a UADE to Preceptis as soon as possible, (but no later than 5 working days after the investigator first learns of the problem). In addition, the investigator may be required to submit a written report to the IRB in accordance with the IRB's specific reporting requirements.

12.0 BENEFIT-RISK ANALYSIS

The potential design benefits of the Preceptis TTI device are as follows:

- Device is designed to make incision and place tube with one pass into the tympanic membrane and ear canal. This is a significant reduction in patient trauma resulting from the 4-6 passes currently required for a standard tympanostomy procedure.
- Device is designed to make an incision that is smaller than those made manually with a standard myringotomy blade and to optimally match the outer diameter of the tympanostomy tube, thereby potentially reducing the extrusion rate of the tube.

- The reduction of trauma and pain to the patient due to reduced passes into the ear canal and manipulation of the ear drum may potentially allow a reduction in the type and amount of anesthesia required for the procedure.

The potential risks or discomforts that may be expected include any of the standard risks of a patient undergoing standard tympanostomy tube surgery. These risks include, but are not limited to, the following:

- Otorrhea,
- Acute tube extrusion,
- Chronic tube extrusion,
- Tube dislocating into the middle ear,
- Tube clogging,
- Bleeding,
- Vertigo,
- Nausea,
- Infection,
- Hearing loss,
- Facial nerve injury.

Other risks may exist. Any additional risks for participation in this study have been minimized by careful patient selection, center selection, and training, as well as by implementing monitoring procedures to ensure proper conduct and management of the study.

14.0 PROTOCOL MODIFICATIONS AND DEVIATIONS

The investigator may not modify this protocol without obtaining written concurrence from the sponsor. The investigator in conjunction with Preceptis will submit protocol modifications to the IRB as necessary.

Any deviations from this protocol intended to protect the physical well-being of a patient are to be reported to Preceptis and the IRB as soon as possible and no later than five (5) working days after the deviation occurred. Other deviations to the protocol must also be reported to Preceptis using the applicable CRF.

15.0 STUDY MATERIALS

Study materials will be provided by the sponsor, Preceptis. Sites will be responsible for the securing, storage, and handling of study materials according to site-specific institutional processes.

16.0 MONITORING PROCEDURES

An employee of the study sponsor, Preceptis Medical, Inc., or its designee, will serve as study monitor. Study monitoring activities will include verification of study data to source documents. Monitors may also assume responsibility for communications between the investigator and the sponsor.

Site visits are performed to ensure that the proper medical records are reviewed and that study data is complete and accurate. Database downloads and study documentation will be compared to source documentation and reviewed for accuracy, completeness, and protocol compliance. The following documents will also be monitored:

- Informed Consent Forms: Informed consent must be signed by each patient. These documents will be monitored 100% to ensure they are in compliance.
- IRB: All approvals, adverse events reports, unanticipated adverse device effect reports, protocol deviations, annual reports and other correspondence with the center's IRB must be up to date and on file. These documents will be monitored 100% to ensure they are in compliance.

Site visits will also be used to verify source data, assess the maintenance of records and reports, assess progress toward meeting study objectives, and identify any concerns that stem from observations of study management documents. Resolution of concerns and completion of corrective actions will be documented by the study monitor in monitoring reports. At the conclusion of the study, a final monitoring visit will occur to appropriately close out the study

ATTACHMENT A (consent forms)

ATTACHMENT B CASE REPORT FORMS

ATTACHMENT C REPORTABLE ANTICIPATED ADVERSE EVENTS

Anticipated AE	**Definition**
Otorrhea	Fluid discharge from the middle ear.
Acute tube extrusion	During the surgical procedure, a myringotomy incision is completed but the tympanostomy tube will not stay in the tympanic membrane.
Chronic tube extrusion	At the initial follow-up visit, the tube is no longer in place in the tympanic membrane.
Tube dislocating into middle ear space	Tube passes completely through the tympanic membrane and falls into the middle ear cavity.
Tube clogging	Tube becomes clogged and fails to provide ventilation and drainage.
Bleeding	Bleeding in the ear canal, tympanic membrane, or the middle ear.
Vertigo	The patient experiences dizziness beyond 72 hours post-surgically.
Nausea	The patient experiences nausea and/or vomiting beyond 72 hours post-surgically.
Infection	Patient has fever $\geq$ 101 F beyond 24 hours post-surgically.
Hearing loss	Hearing loss $\geq$ 15 dB compared to baseline result in Pure Tone Average (PTA).
Facial nerve injury	Any weakness in face or altered perception of taste beyond 24 hours post-surgically.