HUMMINGBIRD® TTS
PRECEPTIS MEDICAL

Investigational Plan for
Pivotal Study of the Preceptis Medical Inc. Hummingbird® Tympanostomy Tube System (H-TTS) in the Otolaryngology Clinic
A Non-Significant Risk Study

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INVESTIGATIONAL PLAN SUMMARY

1.0 BACKGROUND

1.1 Device Name

The Preceptis Hummingbird® Tympanostomy Tube System (H-TTS)

1.2 Device Description

The Hummingbird® Tympanostomy Tube System (H-TTS) 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 otolaryngologists using either local anesthesia (usually adults) or general anesthesia (usually children).

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

1.3 Summary of Previous Clinical Results

285 patients have been treated in an OR or ASC under GA or sedation as part of two prior clinical studies at the University of Minnesota Masonic Children's Hospital, Children's Hospitals and Clinics of Minnesota, and Mayo Clinic. Procedural outcomes and feedback from the otolaryngologists have shown that the H-TTS reduces surgical trauma for the patient as designed. Safety was evaluated by two independent otolaryngologist reviewers, and no safety issues were identified. There were no intra-operative or immediate post-operative adverse events.

Additionally, a feasibility study was initiated in 2017 in up to 20 patients at Health Partners with Dr. Rimell as the PI. The study is evaluating the intra-operative performance of the H-TTS in children from 6-60 months. Twelve (12) children were enrolled in the feasibility study and treated successfully in an office setting with the H-TTS and only local anesthetic. There have been no intra-operative adverse events. Using the H-TTS in an office may be even safer than under sedation or a standard tube procedure under GA since the child's movement can be mitigated in the office environment. Under sedation, there is still some minor movement, and, under GA, patients can still move from a painful stimulus and are frequently restrained with induction or wake up. Due to the positive results of the feasibility study patients, the decision was made to proceed to a larger multi-site assessment.

Enrollment of 225 children (209 6-24 months and 16 5-12 years), for a total of 437 ears have been completed in this Pivotal Clinic Study. Study enrollment was allowed to surpass the goal of 200 enrollments to allow collection of FDA requested patient tolerability videos in the 6-

24 month old group and to give study investigators access to office tube placement due to limited operating room availability during the COVID-19 pandemic. The study results demonstrate the safety, efficacy and tolerability of in-office tube placement in young children using the HTTS, patient restraint, and topical anesthetic. Tubes were successfully placed in the office in 98.9% of the cases (success); the anticipated AE rate was 0.46% and there were no serious AEs reported (safety); and the HTTS successfully delivered the tube across the TM in 97.0% of the ears (efficacy).

1.4 Regulatory Status

The H-TTS has been cleared by the FDA under the following conditions:

- In adults, the H-TTS is cleared for use in any location with any type of anesthetic.
- In children, the H-TTS is cleared for use in a hospital or ASC setting under both general anesthesia and moderate (conscious) sedation.
- In children 6-24 months, the H-TTS is cleared for use in an office setting.

1.5 Indications for Use and Intended Use

The H-TTS is intended to deliver a tympanostomy tube (also referred to as a ventilation tube) through the tympanic membrane of the patient and is indicated to be used in office settings for children 6-24 months old.

2.0 STUDY OBJECTIVES

The objective of this study is to evaluate the safety and performance of the H-TTS for the placement of ear tubes in children 2-21 years old undergoing tympanostomy tube placement in an otolaryngology clinic using local anesthetic and control of patient movement, as applicable.

3.0 STUDY DESIGN OVERVIEW AND DURATION

The study is a continuation of a multi-site, prospective, treatment-only study of the H-TTS to enroll patients 2-21 years old. Enrollment is complete for the 6-24 month old group.

Enrollment in the study at each site will begin after receipt of Institutional Review Board (IRB) approval. The goal is to enroll 30 patients in the 2-4 year old group and 30 patients in the 5-21 year old group at up to 10 clinical sites.

4.0 STUDY ENDPOINTS

4.1 Safety Endpoint

The rate of AEs, and the rates for each specific type of event, will be analyzed.

4.2 Efficacy Endpoint

Efficacy evaluation will consist of determining whether the H-TTS device successfully delivers the tympanostomy tube across the tympanic membrane.

4.3 Success Criteria

Success will be defined as the ability of the surgeon to place ear tubes using the H-TTS device in the office setting with the use of local anesthetic.

5.0 STATISTICAL METHODS AND DATA ANALYSIS

5.1 Data Analysis

Data from the 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 analysis outlined below will be completed first on all subjects aged 2 to 21 years (N=60) and then separately for the subgroups of 2 to 4 years (N=30) and 5 to 21 years (N=30).

The rate of adverse events and the delivery success rate will be calculated, along with corresponding 95% exact confidence intervals which will be calculated using the Clopper-Pearson method.

The adverse events of interest are primarily those specific to the delivery of the tube. These events are acute extrusion of the tube and tube displacement into the middle ear. The proportion of ears experiencing one of these adverse events will be calculated and an exact 95% confidence interval will be constructed about that estimate. These data will be compared heuristically to published AE rates, in particular, to those found in Kay et. al. (2001) who performed a meta-analysis on tympanostomy tube sequelae and to Steele et. al. (2017) published in AHRQ which provides incidence rates for the adverse events of interest. From these two sources of information an expected adverse event rate of 4.5% of ears treated is anticipated. Since the adverse events of interest can also be summarized on a subject basis, the proportion of subjects experiencing an adverse event will also be calculated and 95% exact confidence intervals about that proportion provided. Again, these estimates and confidence intervals will be done separately for each event type.

The proportions of successfully delivered tubes will be calculated, along with the corresponding 95% exact confidence intervals which are constructed using the Clopper-Pearson method. This estimate is on a per ear basis.

The proportion of successful procedures will also be summarized on a per subject basis. A successful subject will be one who has both ears successfully treated. Again, exact 95% confidence intervals will be provided.

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

5.2 Enrollment

A patient will be considered enrolled after informed consent is signed and the incision is made in the tympanic membrane and delivery of the ear tube is attempted with the H-TTS. Inclusion and exclusion evaluation will not require baseline testing and will thus be evaluated prior to signing the consent**.**

Enrollment may begin when the following criteria are met:

- IRB approval of the study protocol and informed consent documents.
- Signed Investigator Agreement-Clinical Study Agreement.

- Investigational site personnel training on the study protocol.
- Inclusion-exclusion criteria met for each patient.

6.0 SAMPLE SIZE

The overall sample size for this study is 60 subjects aged 2 to 21 years. There are two subgroups which will be analyzed separately as outlined in section 5.1. These subgroups are those subjects aged 2 to 4 years and those subjects aged 5 to 21 years.

Adverse events related to delivery of the tube are expected to occur in approximately 4.5% of ears. The width of the 95% confidence intervals will vary between the overall analysis and the analysis of the subgroups. The table below shows the width of the 95% exact confidence intervals for various analyses.

Subject Group	# of Subjects	# of Ears	95% Lower Bound (%)	95% Upper Bound (%)	Confidence Interval Width (%)
Overall	60	120	1.4	9.5	8.1
Subgroup	30	60	1.0	13.9	12.9

The width of the 95% confidence intervals for this endpoint are on a per ear basis. The interval width for the overall analysis is less than 10 percentage points. For the subgroup analysis, the width of the 95% confidence interval is approximately 13 percentage points.

The rate for successful delivery of the tube is expected to be at least 95%. Again, depending on the analysis being done, the width of the exact 95% confidence interval will vary. The table below shows the width of the confidence intervals for the various analyses. These confidence intervals and widths are based on a per ear basis.

Subject Group	# of Subjects	# of Ears	95% Lower Bound (%)	95% Upper Bound (%)	Confidence Interval Width (%)
Overall	60	120	89.4	98.1	8.7
Subgroup	30	60	86.1	99.0	12.9

Again, the width of the 95% confidence interval for the overall analysis is less than 10 percentage points and for the subgroup analysis the width is approximately 13 percentage points.

7.0 PATIENT POPULATION

Selection Criteria

Patients considered for this study must meet all of the inclusion criteria in section 7.1 below. However, if they meet ***any*** of the exclusion criteria in section 7.2, they will not be eligible to participate in the study.

7.1 Inclusion Criteria

Patients must meet *all* of the following:

1. Scheduled to undergo tympanostomy tube insertion in the clinic.
2. Children 2 to 21 years old.
3. Signed parental consent and child assent documents as applicable.
4. Parent is fluent in English

7.2 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., child with developmental delay).
2. Anatomy precludes sufficient visualization and access to the tympanic membrane.

8.0 INVESTIGATOR AND SITE TRAINING

This study is a continuation of the multi-site, prospective, treatment-only study of the H-TTS. All investigators participating in this study have been trained according to previous versions of the protocol. No new sites will be added.

9.0 TYMPANOSTOMY PROCEDURE

The tympanostomy procedure will take place in the otolaryngology clinic. Movement in young children will be controlled as appropriate (i.e. swaddling, papoose board). Parents will be informed and must agree to the methods that will be used to control movement for their child prior to the procedure. All patients will have a local (topical) anesthetic of surgeon's choice (i.e. Phenol) applied to the tympanic membrane prior to insertion of the H-TTS into the ear canal. Medical staff may choose to provide additional analgesics (i.e. Tylenol) per clinic standard of care.

Distraction/comfort techniques may be used per clinic standard of care, and may include, but are not limited to:

- Pre-procedure medication (i.e. Tylenol)
- Presence of parent for the procedure
- Use of media/videos during the procedure

10.0 CONSENT

A parental consent document will be used for all children under 18 years of age. Patients over 18 years of age will sign a consent document. In addition, a child assent document will be used for children 7-17 years of age (age range may be site-dependent). Prior to obtaining consent, the study will be explained to the parents and older children by the investigator or appropriate designee. Parents and assenting children must sign the appropriate consent document(s) prior to enrollment. In addition, a video release form will be required for parents to sign to give permission for the procedure to be audio and video recorded for patient tolerability assessments.

Additionally, personal health information created or received for the purposes of this study is protected under HIPAA. Patients will be required to sign a HIPAA form allowing the

principal investigator, research staff, and Preceptis access to their individual health information. The site may incorporate the HIPAA form within the consent documents.

The consent documents are located in **Attachment A**.

11.0 STUDY PROCEDURES

11.1 Summary of Study Procedures

The Principal Investigator (PI) is responsible for the quality of all data submitted to Preceptis. Documentation of patient eligibility, procedural experience, first follow up visit (approximately 3-10 weeks after the procedure), and adverse events will be collected. (Sample case report forms are in **Attachment B)**

CRFs	Type of Form	Timing
#1	Enrollment	Prior to tympanostomy procedure
#1	Procedure	Time of procedure
#2	AE	As applicable
#3	Parent Survey	Upon completion of procedure and at first follow up visit
#4	Follow Up	First follow up visit after procedure (approximately 3-10 weeks)
#5	Additional Events of Interest	Upon completion of follow up visit

11.1.1 Baseline

Parents of children who require 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. If the patient and parent agree to participate, the appropriate consent documents will be signed. There are no further baseline tests required for the study.

11.1.2 Procedure

Once appropriate written consent has been obtained, the procedure will take place in the ENT (otolaryngology) clinic. Patient demographic and procedure data will be collected. A parent survey will be completed upon completion of the procedure, but the decision to complete the survey is at the discretion of the parent. If a parent opts not to complete the survey, it will not be considered a protocol deviation.

11.1.3 Additional Information Collection

11.1.3.1 Collection of Videotapes for Patient Tolerability Evaluation

Procedures for a sub-set of patients in the 2-4 and 5-21 year old group who provide consent will be audio and video recorded along with their caregivers (if applicable) to evaluate patient tolerability of the procedure at sites with the capability and resources to perform such recordings. The video will begin on patient arrival to the

procedure room and continue until 3 minutes after the procedure has been completed. These video recordings will be independently reviewed by independent observer(s) to evaluate patients using pre-defined descriptors of 4 different levels of behaviors at 5 different time-points of the procedure: 1) when patient enters room and otoscopy (as applicable), 2) after papoose or swaddling, 3) during wax removal (as applicable), 4) during the Hummingbird procedure and 5) three minutes after procedure is completed.

11.1.3.2 Tympanic Membrane Quadrant

The quadrant of the tympanic membrane where the tube was placed will be recorded (e.g., anterior inferior).

11.1.3.3 Additional Events of Interest

Additional events of interest will also be collected. Definitions are included in Appendix D.

11.1.4 Follow Up

Standard of care data will be collected at the first follow up visit (with audiogram or OAE testing if possible) approximately 3-10 weeks after the procedure. The parent survey will be completed again at the follow up visit, but the decision to complete the survey is at the discretion of the parent. If a parent opts not to complete the survey, it will not be considered a protocol deviation. If a patient does not return for any follow up or the follow up is outside of the expected timeframe, it will not be considered a protocol deviation.

11.2 Study Termination

After the last patient has completed the first follow up visit after the procedure (approximately 3-10 weeks), 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.

12.0 ADVERSE EVENTS

Reporting Criteria

All adverse events (AE), both anticipated and unanticipated, will be reported. The event type, treatment, severity, and relationship of the event to the procedure or to the study device will be assessed by the PI performing the procedure. For validation, all AEs will be reviewed by all participating PIs at a clinical site.

Anticipated adverse events and the definitions for serious adverse events are found in Attachment C. Common occurrences (e.g., minor bleeding, purulent discharge) during a tympanostomy procedure are not considered AEs.

13.0 BENEFIT-RISK ANALYSIS

13.1 Benefits

The H-TTS is designed to make an incision and place a tube with one pass through the ear canal and into the tympanic membrane. This has been shown to be a significant reduction in patient trauma compared to the 4-6 passes required for a standard tympanostomy procedure. It also makes the procedure easier for the surgeon particularly in a patient not under general anesthesia. This reduction in trauma is of both benefit to the patient and surgeon because it can reduce the surgical time and the need for anesthetic agents and make placement of a tympanostomy tube under local anesthetic easier for the surgeon.

Additional benefits of using the H-TTS and performance of the procedure in an otolaryngology clinic include: avoiding risks associated with general anesthesia, no NPO restrictions, more cost effective, convenient immediate treatment vs. having to return at a later scheduled date for the procedure (as well as no need for pre- or post-op appointments). The increase cost of both time and money to society of a preoperative visit to primary care prior to general anesthesia is also eliminated.

The position of the American Academy of Otolaryngology – Head and Neck Surgery (AAO-HNS) is that tympanostomy tubes are safe and effective for managing otitis media in children who meet current guidelines for tube insertion. Although insertion of tympanostomy tubes in children is generally accomplished in the operating room under general anesthesia, insertion in the clinic in appropriately selected patients using shared decision making between clinicians and families can be appropriate.

13.2 Risks

Previous clinically studies have demonstrated that the risks for this study are no different from those associated with standard tympanostomy procedures.

Potential risks or discomforts associated with any tympanostomy tube surgery include, but are not limited to, the following: otorrhea, acute tube extrusion, chronic tube extrusion, tube dislocating into the middle ear, tube plugging, bleeding, vertigo, nausea, infection, hearing loss, facial nerve injury.

Older children and adults typically receive ear tubes in a clinic setting using only local anesthetic since they can remain still and tolerate the procedure. In this study, movement will be controlled to prevent motion that could interfere with the procedure while the surgical instruments are in the ears. Except for movement, which will be controlled by the nurse and doctor, the researcher and sponsor are not aware of any risks in this study that are different from normal ear tube procedures in an office setting. Methods to control patient movement in this study are no different than those normally used for children treated in the clinic for a procedure such as removal of a foreign body in the ear or nose or remove cerumen, or to perform such routine procedures as flexible nasopharyngoscopy or flexible laryngoscopy in the clinic.

14.0 PROTOCOL MODIFICATIONS AND DEVIATIONS

The investigator may not modify this protocol without obtaining written concurrence from Preceptis. 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 should be reported according to IRB policies and to Preceptis as soon as possible.

15.0 STUDY MATERIALS

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

16.0 INVESTIGATIONAL DEVICES

For purposes of this study, the H-TTS is considered an investigational device and inventory must be stored in a secure, locked location with limited access. Inventory records must be maintained to document disposition of each device.

17.0 MONITORING PROCEDURES

An employee of Preceptis Medical, Inc., or its designee, will serve as study monitor. At least one monitoring visit will occur prior to conclusion of the study, COVID-19 permitting. Study monitoring activities will include verification of study data to source documents. Monitors may also assume responsibility for communications between the investigator and Preceptis.

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:

- Consent documents: Appropriate consent documents must be signed by each patient/parent. 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 site'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, evaluate 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 close out the study.

ATTACHMENT A CONSENT FORMS

ATTACHMENT B CASE REPORT FORMS

ATTACHMENT C ADVERSE EVENTS

Anticipated AE	Definition
Acute tube extrusion	During the surgical procedure, a myringotomy incision is completed but the tympanostomy tube will not stay in the tympanic membrane.
Tube dislocating into middle ear space and cannot be retrieved	Tube passes completely through the tympanic membrane and falls into the middle ear cavity and is unable to be retrieved (either in the office or in the OR).

SERIOUS ADVERSE EVENT DEFINITIONS

1. Event resulted in death
2. Event was life-threatening
3. Event required new hospitalization (> 24 hours stay)
4. Event required prolonged hospitalization (> additional 24 hours)
5. Event resulted in disability or permanent damage (e.g., permanent hearing loss)
6. Event required medical or surgical intervention to preclude permanent impairment of a body function, or prevent permanent damage to a body structure, ***due to the use of a medical device.***

ATTACHMENT D– Definitions for Additional Events of Interest

Events	Definition
Infection	Infection as defined as: • Patient has fever > 101 F beyond 24 hours post-surgically (per parent feedback) OR • Unusual or excessive TM inflammation OR • Otitis externa
Unintended TM perforation	During the procedure, the surgeon inadvertently creates a perforation in the TM without successfully delivering a tube.
Hearing loss due to damage to middle ear structures	Hearing loss due to procedural damage to the ossicular chain due to the tube being placed in the posterior-superior quadrant.
Abrasion of the external auditory canal	Excessive or unusual abrasion to the external auditory canal at time of procedure.
Ear bleeding	Excessive or unusual bleeding in the ear canal or tympanic membrane that requires epinephrine or oxymetazoline at the time of the procedure.
Medialized or partially medialized tube	Ear tube is medialized or partially medialized at follow-up.
Ear Pain	Excessive or unusual ear pain exhibited by the child or reported by the parent or by the child at follow-up.
Lateral displacement of tube	Lateral displacement of tube during deployment