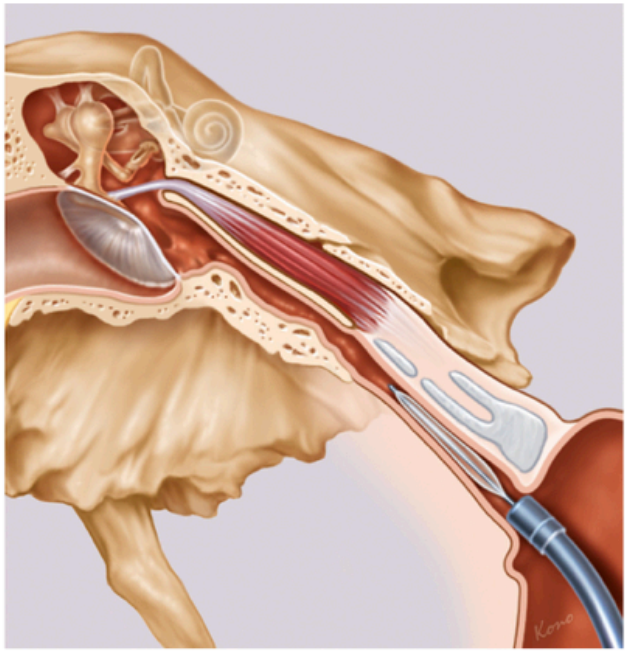
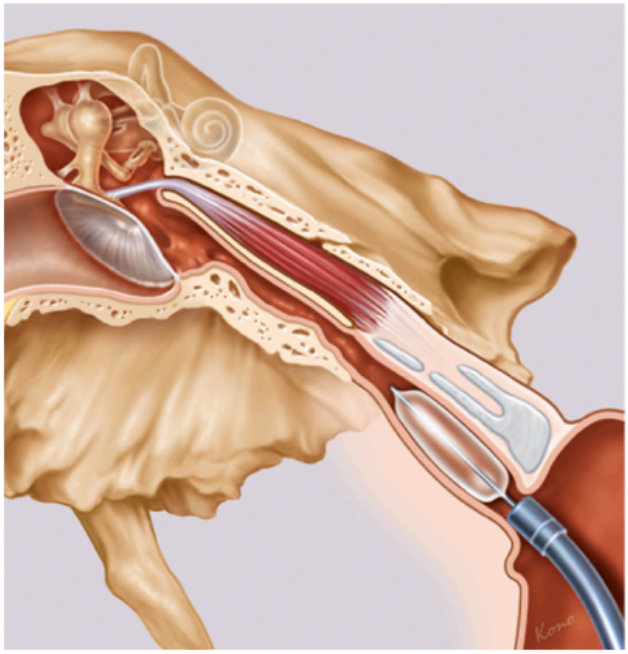
Balloon Dilatation for Eustachian Tube Obstruction: A Randomised Control Trial





Project Protocol
Version 1

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Introduction:

The eustachian tube (ET) constitutes a natural conduit between the middle ear and the nasopharynx and is essential for normal middle ear function and hearing (Figure 1). Eustachian tube dilatory dysfunction (ETDD) is a universal healthcare problem, with an estimated adult prevalence of approximately 1% worldwide, and refers to a physiological disorder of the eustachian tube that results in inadequate ventilation of the middle ear. The exact cause and pathophysiology of ETDD is yet to be elucidated but importantly it is known to be associated with a number of pathological middle ear processes that can result in significant morbidity. Amongst these adverse outcomes are chronic otitis media, tympanic membrane retraction, hearing loss and cholesteatoma.

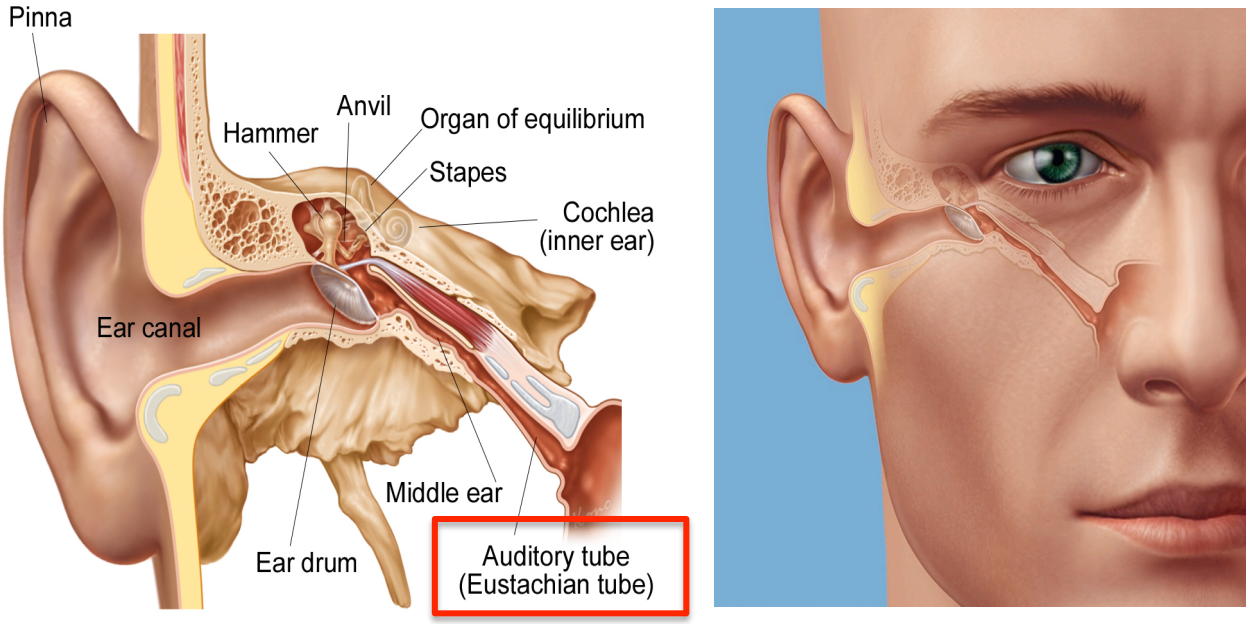

Figure 1. Anatomy and relationships of the Eustachian tube (Image credit: Spiggle and Theis)

A number of treatments have been proposed for the treatment of ETDD including breathing maneovers, pharmacological agents, mechanical devices and nasal surgery though these methods have had limited success and can be ineffective at treating the underlying tubal dysfunction. Moreover, patients with chronic Eustachian tube dysfunction (ETD) may undergo procedures to manage the complications of ETDD, such as the insertion of multiple ventilation tubes (grommets), which themselves can lead to problems like tympanosclerosis, chronic perforation and cholesteatoma.

In recent years catheter assisted balloon dilatation of the eustachian tube (BDET) has been undertaken as a means of improving middle ear ventilation and eustachian tube compliance with safety and success for the treatment of persistent ETDD. The procedure involves transnasal insertion of a non-compressible balloon into the cartilaginous portion of the ET, after which the balloon is inflated under pressure in a controlled fashion for a period of time (usually 2 minutes) (Figure 2). The balloon is then deflated and removed. The procedure is already being undertaken across Australia and internationally.

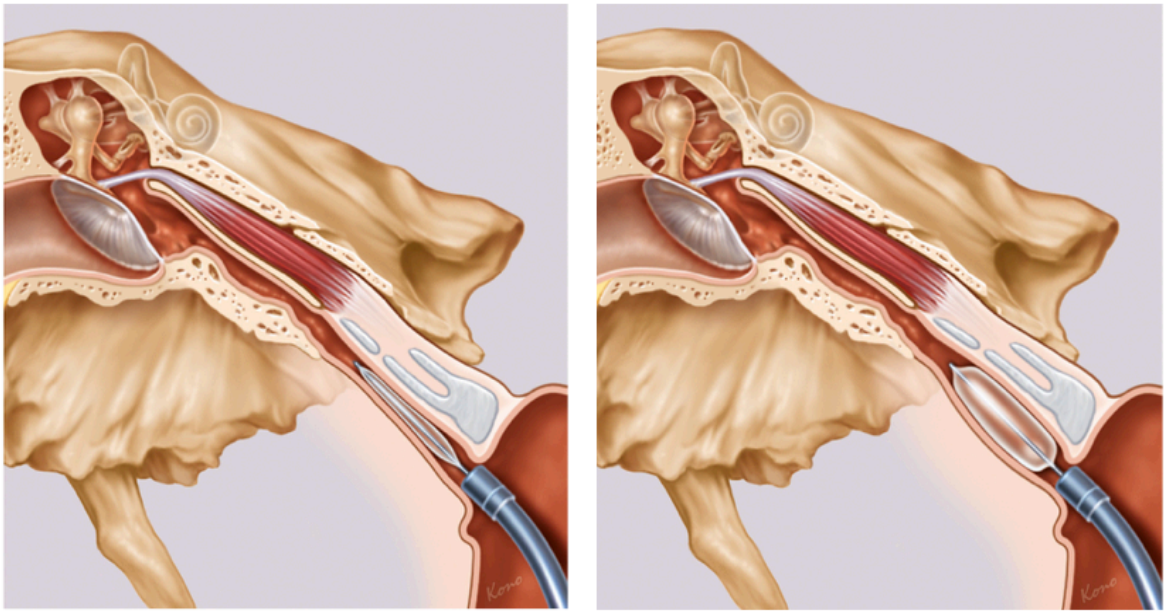

Figure 2. Introduction, positioning and inflation of the Eustachian tube balloon catheter with resultant dilatation of the eustachian tube (Image: Spiggle and Theis)

To date there have been several case series without controls detailing successful outcomes using BDET as well as a single recent randomised control trial undertaken by Poe et. al. using a particular balloon system (Acclarent Inc., Irvine, California). These studies have reported improvement in clinical outcomes commonly used to assess and diagnose ETDD such as tympanometry and Eustachian Tube Dysfunction Questionnaire-7 Symptom (ETDQ-7) scores (Appendix 1).

The proposed randomized control trial is modeled on the randomized control trial performed by Poe et. al but aims to assess a similar balloon system utilised for BDET made by Spiggle and Theis Medizintechnik,. Like Poe et. al., this course of investigation is undertaken in an effort to determine the relative efficacy of the particular balloon system when combined with medical management of persistent ETDD compared with medical management alone. As well as to establish the efficacy of BDET in the treatment of ETDD in an Australian population and compare these findings to previously published data.

Aims:

1. To compare the efficacy of the Spiggle and Theis Medizintechnik eustachian tube balloon catheter system (Tubavent) combined with medical management versus medical management alone in the treatment of obstructive ETDD.

2. To compare the results obtained using the Tubavent with the available literature.

3. To evaluate the efficacy of BDET for the treatment of ETDD in an Australian population.

The Device:

This study will employ the Spiggle and Theis Medizintechnik balloon catheter system designed specifically for the purpose of dilatation the ET in the setting of dilatory dysfunction. The system has 3 components, the smooth tipped balloon catheter, the included introducer and an insufflator. All components of the system have received Therapeutic Goods Administration (TGA) approval in Australia for use in the proposed procedure (see additional documents).

Components required:

1. Eustachian tube balloon catheter
2. Angled Introducer
3. Insufflator

The device is utilized in an anaesthetised patient and involves the use of all 3 components. After the patient is asleep the nasal cavity is prepared using a decongestant and the system in systematically deployed in a standardized way via the nasal cavity on the affected side.

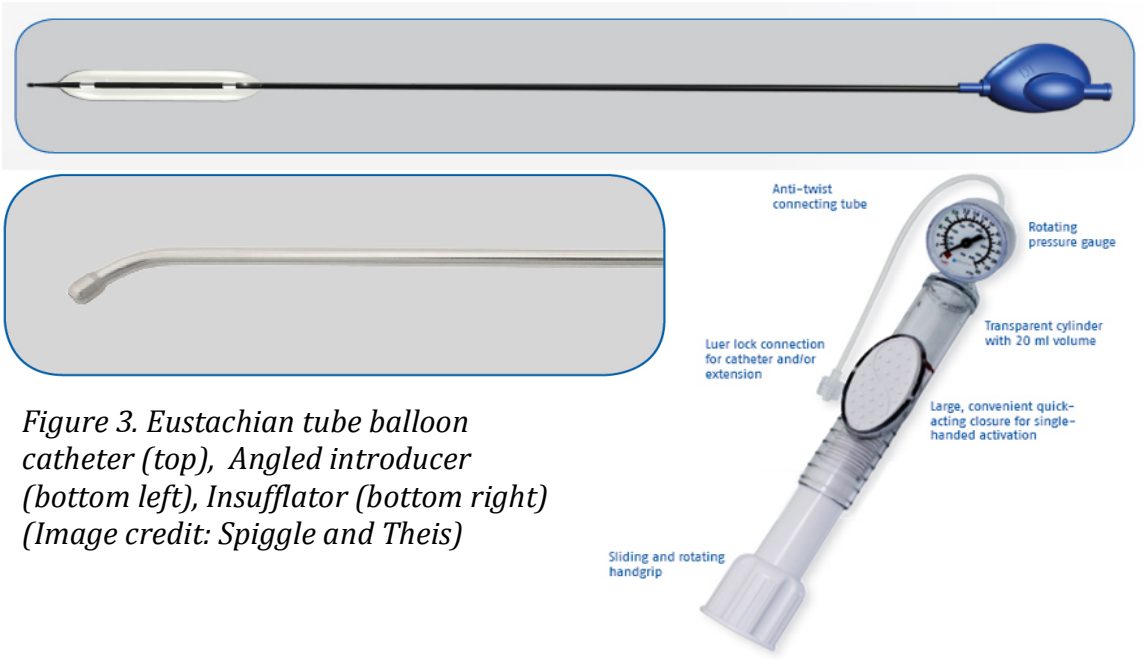

Figure 3. Eustachian tube balloon catheter (top), Angled introducer (bottom left), Insufflator (bottom right) (Image credit: Spiggle and Theis)

The procedure is performed entirely under endoscopic guidance/visualisation. First, an introducer with an angled tip that allows it to be directed towards the ET is inserted through the nose towards the opening of the ET. The balloon tipped catheter is then inserted through the introducer until the tip is just seen at the distal portion of the introducer near the Eustachian tube opening. By manipulation of the introducer, the atraumatic smooth tip of the balloon catheter is introduced into the tubal orifice. The balloon catheter is then advanced and locked into the introducer. The extension of the balloon catheter is limited by design and the locking mechanism to prevent it being advanced too far into the ET. Once locked into the introducer, the balloon is then inflated using a specific insufflator that utilized sterile saline for the inflation of the balloon (insufflator attached to the balloon catheter using a luer lock connector). The balloon is inflated to a specific pressure (usually 10atm) and monitored using a barometer on the insufflator. The pressure is maintained for a period of 2 minutes before the balloon is deflated, withdrawn into the introducer and the device is removed under endoscopic visualisation.

In the case of bilateral disease, 2 separate procedures take place, via each nasal cavity to dilate each individual ET, utilising the same balloon, which can generally be redeployed on the second side.

Materials and Methods:

Study Design:

The proposed study is a prospective multicenter, non-significant risk, randomised control trial that has been designed to demonstrate the superiority of BDET using a eustachian tube balloon catheter plus medical management when compared to medical management alone for the treatment of ETDD.

Study Sites

The study will be undertaken at several hospitals within the Sydney area, they are:

- North Shore Private Hospital
- Royal North Shore Hospital
- The Mater Hospital (North Sydney)
- Chatswood Private Hospital
- Macquarie University Hospital
- Hunters Hill Private Hospital
- Norwest Private Hospital
- Castlecrag Private Hospital

Participants:

Participants randomised as part of the study will be patients who present to one of the surgeons involved in the study and meet the inclusion criteria while not being subject to exclusion based on the following:

Inclusion criteria

To be eligible to enroll in the study patients must:

- Provide informed consent to participate in the study
- Have a diagnosis of persistent ETDD
    - A positive diagnosis is confirmed by the presence of abnormal tympanometry and symptomatic dysfunction as documented by the ETDQ-7 questionnaire mean item score ≥ 2.1, for 12 weeks or more prior to enrollment in the study
- Be 22 years of age or older with persistent ETDD and have failed medical management consisting of either 4 weeks of continuous daily usage of intranasal corticosteroids spray or a minimum of 1 completed course of oral steroids within 90-days prior to study enrollment.
- Have a recent (or be able to undergo a) CT petrous temporal bone
- Be able to undergo fibreoptic nasendoscopy

Exclusion criteria

Exclusion criteria include the following:

- Anatomy that requires an adjunctive surgical procedure
- Planned concomitant nasal, sinus or ear procedures during the study
- History of major head and neck surgery within 4 months or randomization
- History of head and neck radiation
- Diagnosis of patulous eustachian tube
- Fluctuating sensorineural hearing loss
- Active acute or chronic otitis media

- Tympanic membrane perforation or the presence of a tympanostomy tube (grommet)
- Presence of tympanosclerosis
- Acute upper respiratory tract infection
- Active temporomandibular joint disorder
- Cleft palate or a history of cleft palate repair
- History of craniofacial syndrome
- History of cystic fibrosis
- History of ciliary dysmotility syndrome
- History of systemic mucosal diseases or immunodeficiency disorders
- Intolerance of protocol-defined medication regimen
- Prior surgical ET intervention
- Limited dilatory muscular contractions on endoscopy of the ET
- Contraindications to BDET

Consent:

Prior to enrolling in the study, participants will be required to provide informed consent. To allow this process to occur, all patients who meet the eligibility criteria to be included in the study will be notified about the study and its aims by the consulting surgeon. Additionally, they will receive an information sheet about the study. For those with a primary language other than English, an accredited translator will be used to deliver this information.

Patients will not be incentivised or coerced into enrolling in the study and no treatment options will be restricted if they choose not to participate. Potential participants will be given sufficient time to consider the information they have been given prior to making a decision about whether to be involved in the study. Participants need not necessarily make their decision to participate in the study on the day of consultation and will be able to consider their involvement further if they choose to. The consulting surgeon will answer any questions that a potential participant has. A participant's consent will be formalized by way of a specific consent form used for the purpose of the study detailing the requirements of their involvement in the project as well as the known and potential risks (see additional documents).

Importantly, participant consent can be withdrawn at any time without any bearing on the therapeutic relationship between the consulting surgeon and the patient.

Data sources:

The data collected in the study will come from several sources at different time intervals throughout the study (Table 1), namely, pre-intervention and at several follow up intervals. The sources of data will be acquired from otoscopic examination, tympanometry, nasendoscopy, and ETDQ-7 scores (Appendix 1).

- **Otoscopy**
  - Otoscopy is part of the routine ENT assessment and examination of the ear.
  - Otoscopy involves the use of an otoscope to directly visualize, examine and assess the external auditory canal and tympanic membrane
  - Otoscopy will take place at baseline, 2, 6, 12 and 24 week follow-up appointments

- **Tympanometry**
  - Tympanometry is obtained as a part of a pure tone audiogram (hearing test) and is a test of middle ear functioning. It looks at the compliance of the tympanic membrane to changing pressures, indicating how effectively sound is transmitted into the middle ear.
  - Tympanometry will take place at baseline, 6, 12, and 24 week follow-up

- **Nasendoscopy**
  - Nasendoscopy is part of the routine ENT examination and involves fibreoptic examination of the nasal cavity and nasopharynx under topical nasal anesthesia.
  - Nasendoscopy will take place at baseline, during the procedure, 2, 6, and 24 week follow-up appointments.

- **Eustachian Tube Dysfunction-7 Questionnaire (EDTQ-7)**
  - The ETDQ-7 is a validated questionnaire for the assessment of patient reported symptoms strongly associated with Eustachian tube dysfunction and pathology
  - EDTQ-7s will be undertaken at baseline and at 6, 12 and 24 weeks follow up appointments.

	Baseline	2 week follow-up	6 week follow-up	12 week follow-up	24 week follow-up
Otoscopy	✓	✓	✓	✓	✓
Tympanometry	✓		✓	✓	✓
Nasendoscopy	✓	✓	✓		✓
ETDQ-7	✓		✓	✓	✓

Table 1. Time course of Investigations and follow up intervals

Sample Size and Randomisation:

75 patients who meet the inclusion criteria for the study will be randomized following their informed consent. This will be undertaken using a computer based randomization program in a ratio of 2:1 (50:25) to receive either BDET with a balloon catheter plus medical management (Group 1, n=50) or medical management alone (group 2, n=25).

Randomization will be stratified by baseline tympanogram type such that equal numbers of patients with baseline type B and C tympanograms (abnormal results) are assigned to each group. In patients with unilateral symptoms, treatment will be confined to the affected ear. When bilateral treatment is indicated and the subject has two different abnormal tympanogram scores, the patient will be stratified to type B.

Proposed Interventions and Treatment Arms:

Group 1 (balloon dilatation + medical management)

Balloon dilation of the ET will be performed under general anesthesia in the operating room by trained and accredited otolaryngologists as recognized by the Royal Australian College of Surgeons (RACS). All of the surgeons involved in the study are skilled in the proposed procedure and have performed multiple successful balloon dilatations of the eustachian tube for the treatment of ETDD prior to the commencement of the study.

Each ET dilatation will be performed using a standardized technique. Patients will receive general anesthesia by a accredited anaesthetist. The nasal cavity on the affected side will be decongested using 3mls of oxymetazoline instilled into the nasal cavity. If the patient is undergoing bilateral dilatation then both nasal cavities will be decongested. Rigid nasendoscopy will be used in all cases to allow examination of the nasal cavity and facilitate safe and accurate placement of the balloon catheter into the ET.

With the aid of nasendoscopy, a single use introducer will inserted into the nasal passage on the affected side so that is passes to the back of the nasal cavity and nasopharynx. The angled introducer is then pointed towards the affected ET opening. A single use catheter with a balloon tip is then inserted through the introducer and emerges from the angled end into the opening of the ET. The catheter is then advances into the ET under visualization until the indicator line on the catheter emerges from the introducer, signifying that the catheter has been sufficiently advanced. The balloon is then inflated with sterile isotonic saline solution (NaCl 0.9%) for a period of 2 minutes using the included insufflator, to an inflation pressure of 10 to 12 atmospheres while the balloon is held in situ. At the conclusion of the 2-minute period, the balloon is deflated and pulled back out of the ET so that it re-enters the introducer. The balloon catheter and introducer are then removed together form the nasal cavity. If the patient has bilateral disease and both ETs require treatment, the procedure is repeated on the other side in the same way.

For patients randomized to receive BDET in conjunction with medical management, medical management was initiated on the day of surgery. Participants will be prescribed a regimen of mometasone nasal steroid spray (Brand name: Nasonex), consisting of two sprays to each nostril once per day for a period of 6 weeks time. Participants will be educated on how to effectively undertake this by their surgeon. After 6 weeks, continuation of medical therapy will be at the discretion of the patient's surgeon.

Group 2 (medical management alone)

Patients randomized to medical management alone will commence the same mometasone nasal steroid spray regimen for a planned period of 6 weeks on the day of randomisation. Again, continuation of therapy after the 6-week period will be at the discretion of the patient's surgeon.

Throughout the duration of study participation, subjects will be permitted to continue any concomitant medications for their ETDD or other medical conditions (i.e., allergic rhinitis, laryngopharyngeal reflux) deemed clinically necessary, per their surgeon's discretion. Subjects will not be permitted to start any new medications or to increase the dose or frequency for existing concomitant medications. Patients requiring such alterations or the commencement of new medications for medically indicated reasons will be excluded from the study.

Intervention Risks:

To date there have been no serious complications reported in the literature associated with BDET. Complications of the procedure are rare and no major complications have been reported. The dilatation will be performed under general anaesthesia and so patient discomfort and distress will be greatly mitigated.

Reported complications include bleeding, surgical emphysema (air bubbles) of the parotid (angle of jaw) region (0.2% chance and temporary in every case) and temporary tinnitus. Although rare, any procedure involving the ear carries a risk of increased hearing loss, dizziness, tinnitus and facial palsy.

Potential complications (that have not been reported so far) include: regional nerve damage, ossicular disruption/hearing loss, carotid artery injury and associated cerebrovascular accident. All of these risks will be discussed as part of the informed consent procedure.

Follow up and Therapeutic Cross Over

Patients will be followed up at 2, 6, 12, and 24 week intervals, examination and diagnostic testing will take place at each of these time point as detailed in Table 1.

At the 6-week follow up, participants initially randomized to the control group will be given the opportunity to cross over to the intervention group in consultation with their consulting surgeon. After crossover, participants will be followed up at the post intervention intervals of 2, 6, 12, and 24 weeks and undergo the testing and examination as outlined in table 1. Participants who chose to crossover will be consented for the procedure and informed regarding the required follow up.

End Points and Statistical analysis

The **primary** effectiveness endpoint will be normalization of tympanometry (to type A) at 6-week follow-up.

Investigators and a blinded, independent evaluator, unaffiliated with the patients' care will review all tympanograms. When findings between investigator and evaluator area inconsistent, a second independent evaluator will conduct a tie-breaking assessment. Each patient will serve as the unit of analysis; for a bilaterally treated patient, both ears tympanograms have to normalise for that patient to be considered a success.

The **secondary** end point will be normalisation of ETDQ-7 scores (<2.1) at 6-week follow up.

Data from all investigations undertaken will be collated at each follow up appointment for each patient. Analysis of the collated non-identifiable data will be undertaken using a statistical analysis package (e.g. SPSS)

Publication and Dissemination:

The findings of the proposed research project will be submitted for consideration of publication in peer-reviewed otology specific and general otolaryngology journals. The content will also be disseminated via presentation at regional, national and international meetings.

Conflicts of Interest:

None of the investigators have any conflicts on interests associated with the proposed research project.

The Seven-Item Eustachian Tube Dysfunction Questionnaire.

Over the past 1 month, how much has each of the following been a problem for you?	No Problem			Moderate Problem		Severe Problem	
1. Pressure in the ears?	1	2	3	4	5	6	7
2. Pain in the ears?	1	2	3	4	5	6	7
3. A feeling that your ears are clogged or "under water"?	1	2	3	4	5	6	7
4. Ear symptoms when you have a cold or sinusitis?	1	2	3	4	5	6	7
5. Crackling or popping sounds in the ears?	1	2	3	4	5	6	7
6. Ringing in the ears?	1	2	3	4	5	6	7
7. A feeling that your hearing is muffled?	1	2	3	4	5	6	7

Reference: McCoul, E. D., Anand, V. K., & Christos, P. J. (2012). Validating the Clinical Assessment of Eustachian Tube Dysfunction: The Eustachian Tube Dysfunction Questionnaire (ETDQ-7). *The Laryngoscope*, *122*(5), 1137–1141. http://doi.org/10.1002/lary.23223

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