

# PROTOCOL

## PreVenT-O

Preventing paediatric middle ear Ventilation Tube  
Obstruction with topical ciprofloxacin (PreVenT-O) : a  
randomised controlled trial

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Date of change	Summary of changes

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### Statement of Compliance

This document is a protocol for a research project. This study will be conducted in compliance with all stipulation of this protocol, the conditions of the ethics committee approval, the NHMRC

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**HREC Number:** HREC/18/MonH/182

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National Statement on ethical Conduct in Human Research (2007) and the Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95).

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## PROTOCOL SYNOPSIS

<i>TITLE</i>	Preventing Paediatric Middle Ear Ventilation Tube Obstruction with topical ciprofloxacin (PreVenT-O) : a randomised controlled trial
<i>OBJECTIVES</i>	<p>3.1 Primary objective</p> <p>The primary objective of this study is to evaluate the impact of two different prophylactic regimens of topical ciprofloxacin otic drops on preventing ventilation tube obstruction in paediatric patients receiving bilateral middle ear ventilation tube placement compared with no prophylaxis.</p> <p>3.2 Secondary objectives</p> <p>The secondary objectives of this study are:</p> <ul style="list-style-type: none"> <li>• To evaluate the impact of two different prophylactic regimens of topical ciprofloxacin otic drops on preventing ventilation tube otorrhoea in paediatric patients receiving bilateral MEVT placement compared with no prophylaxis.</li> <li>• To assess the impact of topical ciprofloxacin prophylaxis on quality of life (QoL) and audiometry results of paediatric patients receiving bilateral MEVT placement</li> <li>• To assess the cost-effectiveness of topical ciprofloxacin otic drops on preventing ventilation tube obstruction in paediatric patients receiving bilateral MEVT placement</li> <li>• To assess whether intraoperative factors may contribute to the occurrence of ventilation tube obstruction.</li> </ul>
<i>DESIGN</i>	<p>The study will be a randomised, examiner-blinded, prospective controlled interventional trial. 360 subjects will be recruited and randomised to three groups; one control and two interventional.</p> <p>Outcomes will be collected during the initial baseline visit as well as at the 6-week postoperative review visit. Data will also be collected through an intraoperative worksheet completed during surgery and a patient diary to be completed in the two weeks following surgery.</p>
<i>OUTCOMES</i>	<p>(1) Incidence of middle ear ventilation tube obstruction at 6 weeks diagnosed by otoscopy and tympanometry.</p> <p>(2) Incidence of middle ear ventilation tube otorrhoea at 2 weeks and 6 weeks by otoscopy.</p>

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	<p>(3) Difference in validated disease-specific QOL (OMO-22) at booking, 2 weeks and 6 weeks post-op.</p> <p>(4) Difference in audiometry pre-op and 6 weeks post-op.</p> <p>(5) Correlation between intraoperative factors and ventilation tube obstruction and otorrhoea.</p> <p>(6) Cost-effectiveness.</p>
<b>STUDY DURATION</b>	12 months
<b>INTERVENTIONS</b>	<p>(1) Control</p> <p>(2) One intraoperative dose of ciprofloxacin otic</p> <p>(3) One intraoperative dose and 5 day course of ciprofloxacin otic</p>
<b>NUMBER OF PARTICIPANTS</b>	360, 120 per arm
<b>POPULATION</b>	Paediatric (17 and under), who are undergoing bilateral myringotomy and ventilation tube placement, with a diagnosis of otitis media with effusion for at least 3 months or recurrent acute otitis media.

## GLOSSARY OF ABBREVIATIONS

ABBREVIATION	TERM
AE	Adverse Event
AOM	Acute Otitis Media
DMC	Data Monitoring Committee
HREC	Human Research Ethics Committee
ITT	Intention To Treat
MEVT	Middle Ear Ventilation Tube
NHMRC	National Health and Medical Research Council
OMO-22	Otitis Media Outcome - 22 QoL Questionnaire
OME	Otitis Media with Effusion
QoL	Quality of Life
VTO	Ventilation Tube Obstruction (Grommet Lumen Obstruction)

## 1. ADMINISTRATIVE INFORMATION

### 1.1. Trial registration

#### 1.1.1. Registry

### 1.2. Expected duration of study

The study is expected to run for 12 months. This is based on a conservative recruitment rate of 10 patients per week, which will require a total of 36 weeks for recruitment, plus a follow-up period of 12 weeks, from initial baseline visit to the 6-week postoperative review visit.

### 1.3. Contributorship

Name	Summary of contribution
Debra Phyland	Lead Investigator, Supervision, project governance and editor
Charles Giddings	Lead Investigator, Supervision, project governance and editor
Chenkan Wang	Associate Investigator, Contributed to protocol

## 2. INTRODUCTION AND BACKGROUND

### 2.1. Background and rationale

One of the most common surgeries performed on children in Australia is middle ear ventilation tube (MEVT) placement with 34065 operations performed in 2012-13. (Australian Atlas of Healthcare Variation 2015) Ventilation tubes or “grommets” are used to restore hearing in children with chronic otitis media with effusion (OME) and as a preventative measure for recurrent acute otitis media (AOM). It works by equalising the pressure in the middle ear and allowing middle ear fluid to drain from the cavity.

A common and frustrating complication of MEVT placement is ventilation tube obstruction (VTO) affecting approximately 11% of patients. Presence of middle ear secretion at surgery is recognised as a major risk factor for VTO. (1) Early VTO occurring before 4 weeks may occur due to bleeding, presence of mucoid secretions during the myringotomy procedure or continued drainage of fluid after the MEVT placement called post-operative otorrhoea. Delayed VTO is typically due to the accumulation of inflammatory eosinophilic cells and squamous epithelial casts.(1-3) The resulting blockage leads to the accumulation of middle ear fluid causing discomfort and reduced hearing. It is hence important to prevent VTO. Preventing VTO also circumvents additional intervention for the child, avoiding exposure to potentially ototoxic hydrogen peroxide drops used to clear blocked tubes or instrumentation with suction catheters in clinic as well as the potential need for revision surgery under general anaesthetic.

Authors have described a variety of interventions to prevent tube blockage. The effect of topical antibiotic/steroid combinations has been investigated with certain drops behaving better than others; Framycetin-Gramicidin/Dexamethasone and Trimethoprim-Sulfamethoxazole/Prednisolone are significantly better at preventing blockages compared to control, whilst Neomycin/Betamethasone was ineffective and did not achieve significant effect. (4-6) It is not known which mechanism of action

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is responsible for preventing tube occlusion. (4) No authors have investigated the effects of topical antibiotics alone in preventing tube occlusion.

Three authors assessed mucosal decongestants, xylometazoline and phenylephrine, which work by controlling tympanic membrane bleeding perioperatively. Both interventions were significantly more effective than control at preventing tube blockage. (7-9) Kumar et al. concluded that xylometazoline was equivalent to ciprofloxacin otic drops in preventing postoperative otorrhoea and ventilation tube obstruction. Other authors assessed different tube coatings (phosphorylcholine, antibiotic, human serum albumin). (10-12) Of which, human serum albumin (HSA) was the only coating which significantly reduced blockage rates.

Interestingly, a case series and retrospective study found a significant association between the commonly used Ciprofloxacin/Dexamethasone ear drops and tube occlusion. They hypothesised that the high viscosity of the drops may lead to crystallisation in the lumen of the tubes leading to more tube occlusions when using Ciprofloxacin/Dexamethasone. (2, 13) However, there may be significant flaws with the findings from Jeon et al. owing to its retrospective design. It is unknown whether the addition of steroids has a synergistic effect on the incidence of occlusion and other sequelae of surgery such as post-operative otorrhoea.

This review of literature highlights the need for high quality evidence regarding the use of interventions for preventing tube blockages.

There is currently no standard of care for prophylaxis around time of surgery, and prescription of drops is surgeon dependent. Topical antibiotic drops given intraoperatively and a short course after surgery is currently preferred by surgeons to prevent VTO and post-operative otorrhoea. Topical antibiotics work by treating the active infection which can reduce the amount of discharge that is produced by the middle ear mucosa. Nawasreh et al. concluded that a single dose of Ciprofloxacin otic drop is as effective as a prolonged 5-day course at preventing otorrhoea but did not report on blockage rates. (14) However, there were severe study limitations due to being poorly powered from its low sample size of 150 patients.

This study seeks to add to data on endpoints of previous studies while investigating ventilation tube obstruction as a primary endpoint. We will be comparing the effectiveness of single dose of Ciprofloxacin ear drops against a 5-day course against control at preventing VTO. Single dosing may have advantages of limiting exposure to quinolone antibiotics and the theoretical increased risk of tympanic membrane perforation. (15)

## 2.2. Aim(s)

The aim of this study is to investigate the efficacy and rationale for routine topical antibiotic prophylaxis (Ciprofloxacin) for the prevention of Ventilation Tube Obstruction in Middle Ear Ventilation Tube placement (myringotomy and ventilation tube placement).

## 4 STUDY OBJECTIVES

### 4.1 Primary objective

The primary objective of this study is to evaluate the impact of two different prophylactic regimens of topical ciprofloxacin otic drops on preventing ventilation tube obstruction in paediatric patients receiving bilateral middle ear ventilation tube placement compared with no prophylaxis.

## 4.2 Secondary objectives

The secondary objectives of this study are:

- To evaluate the impact of two different prophylactic regimens of topical ciprofloxacin otic drops on preventing ventilation tube otorrhoea in paediatric patients receiving bilateral MEVT placement compared with no prophylaxis.
- To assess the impact of topical ciprofloxacin prophylaxis on quality of life (QoL) and audiometry results of paediatric patients receiving bilateral MEVT placement
- To assess the cost-effectiveness of topical ciprofloxacin otic drops on preventing ventilation tube obstruction in paediatric patients receiving bilateral MEVT placement
- To assess whether intraoperative factors may contribute to the occurrence of ventilation tube obstruction.

## 5 STUDY DESIGN

### 5.1 Type of Study

This is blinded, randomised controlled trial of ciprofloxacin otic drops for prophylaxis of early ventilation tube obstruction in a paediatric population undergoing bilateral MEVT placement.

There will be two treatment groups and one control group. 360 participants will be allocated in a 1:1:1 ratio through block randomisation in blocks of 12. Participants will be randomised to receive either no treatment, treatment at time of surgery or treatment for five days after surgery in addition to treatment at time of surgery. For the no treatment and treatment at time of surgery groups, both patients and observers will be blinded from the treatment allocation, whereas for the multi dose group, only the observer is blinded from the treatment allocation while patients will be unblinded.

### 5.2 Study Setting

The study will be based at four academic teaching hospitals (Monash Children's Hospital, Moorabbin Hospital, Dandenong Hospital, Casey Hospital) that are part of Monash Health in Melbourne, Australia.

## 6 PARTICIPANTS AND RECRUITMENT

### 6.1 Number of Participants

360 paediatric participants will be recruited from ENT outpatient clinics within Monash Health.

### 6.2 Eligibility Criteria

Patients will be assigned to a randomised study treatment only if they meet all the inclusion criteria and none of the exclusion criteria.

#### 6.2.1 Inclusion criteria

Each patient must meet all of the following criteria to be enrolled in this study:

- Is between the ages of 1 and 17 years at the time of randomisation
- Has clinically diagnosed recurrent acute otitis media of more than 3 episodes in 6 months or 4 episodes in 12 months, chronic otitis media with effusion lasting for more than 3 months
- Is requiring bilateral MEVT placement with or without adenoidectomy/tonsillectomy
- Has a legally acceptable representative capable of understanding the informed consent document and providing consent on the participant's behalf

- No restrictions apply to weight, gender, ethnicity or prior MEVT placement

#### 6.2.2 Exclusion criteria

Patients meeting any of the following criteria will be excluded from the study:

- Has a known hypersensitivity to quinolone antibiotics or ingredients in ciprofloxacin otic drop
- Has a recent history within 2 weeks of surgery date of acute otitis media treated with topical antibiotics

#### 6.3 Recruitment and identification of potential participants

All potential patients will be recruited from ENT outpatient clinics within Monash Health on their initial preoperative baseline visit or at the date of surgery. Parents and guardians of patients who meet the inclusion criteria will be invited to participate in the trial. They will receive an invitation letter sent with the surgery pack prior to surgery and then by trained staff with appropriate knowledge of the procedure and interventions at the preoperative baseline visit or at the time of surgery. Information about the study will be explained to them by a trained member of staff and a Patient Information and Consent Form (PICF) will be provided. The parent/guardian will then be asked to complete a preoperative questionnaire along with routine surgical preoperative checklist. If the patient or parent/guardian do not wish to participate in the study, they will not enter the trial and receive standard care at our centres. If the participants meet any of the exclusion criteria, they will exit the trial and receive standard care at our centres.

Once patients have been recruited, they will be given a Participant Information document and a letter to GP at the baseline visit. They will be given their patient diaries at the date of surgery and given post-operative instructions.

#### 6.4 Consent

Prior to performing any study specific procedure (including screening procedures to determine eligibility), a signed consent form will be obtained for each participant. For participants below the legal age, a parent, legal guardian, or person with power of attorney, must also sign a consent form. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. The investigator will conduct the informed consent discussion and will check that the participant and their legally acceptable representative comprehend the information provided and answer any questions about the study. Consent will be voluntary and free from coercion. The investigator that conducted the consent discussion will also sign the informed consent form. A copy of the consent form will be given to the participant or their legally acceptable representative and the fact that the participant has been consented to the study will be documented in the participant's record. When the all the inclusion/exclusion criteria have been addressed and the eligibility of the participant confirmed, the participant may be assigned to a randomisation treatment in the study

## 7 INTERVENTION

### 7.1 Treatment arms

All groups will receive bilateral MEVT placement according to standard protocols at our hospital site. This involves making an anteroinferior incision in the pars flaccida of the tympanic membrane and

drainage of the middle ear effusion with a suction catheter and placement of a Shah type middle ear ventilation tube. An intraoperative dose of ciprofloxacin otic drops will be placed into the ear canal if the participant is in the treatment groups. Cotton wool will be placed in the ear canal following the completion of surgery. All patients will be instructed to follow routine post-operative advice about water precaution. Participants are to avoid submerging their heads in water for the first three days and to use earplugs or blu-tac if water contact is required after three days.

In the single dose group, after MEVT placement, 3 drops of ciprofloxacin 0.3% otic drops in each ear at the time of surgery.

For patients in the multi dose group, they will receive a 5 day course of ciprofloxacin 0.3% otic drops in each ear in addition to the 3 drops of ciprofloxacin at the time of surgery.

For patients in the control group, they will receive no treatment.

## 7.2 Intervention

Ciprofloxacin 0.3% otic solution, supplied by Novartis Pharmaceuticals Australia Pty Limited under brand name CILOXAN™, will be used for the two treatment groups.

In the control group, patients will not receive treatment during or after the surgery.

### 7.2.1 Dosage and route of administration

Ciprofloxacin 0.3% otic solution is administered topically into the ear canal. A single dose is 3 drops instilled into the ear canal followed by tragal pressure. The concentration of ciprofloxacin is 3mg/1ml. The dose will not differ between study groups.

In the single dose group, after MEVT placement 3 drops of ciprofloxacin 0.3% otic drops will be instilled into the ear canal with the ear perpendicular to the floor. Tragal pressure, pressing down on the tragus to increase ear canal pressure, will be performed 3 times to ensure penetration of the antibiotic solution into the middle ear space through the ventilation tube. This will be repeated for the opposite ear.

In the multi dose group, patients will receive 3 drops of ciprofloxacin 0.3% otic drops in each ear at the time of surgery. In addition, they will receive one dose of ciprofloxacin 0.3% otic drops twice a day in each ear for a total of 5 days after the surgery. Patients will be instructed to administer the two doses 8 hours apart from each other. Patients will be instructed warm the bottle with their hands before administering the drops and to lie with their ear perpendicular to the floor for 1 minute after administering the drops. Drops can be taken with or without food and there are no restrictions.

### 7.2.2 Dose modification

If patients in the multi dose group, have an adverse reaction to the medication then they are to stop taking the drug and contact the investigator immediately as according to Section 10.2.

### 7.2.3 Preparation and administration of study drug

The study drug is available in a dropper bottle. Patients in the multi dose group will administer the study medication at home and store in a cool place away from direct sunlight. The pharmacy will be responsible for dispensing the medication.

### 7.2.4 Dispensing and product accountability

For the control group, ciprofloxacin otic drops will not be dispensed.

For the intraoperative dose group, a new bottle of ciprofloxacin otic drops will be opened in theatre and 5 drops will be placed into the ear canal by the OR nurse through the ear speculum. This will then be recorded in the operative notes that 5 drops of ciprofloxacin otic was placed into each ear canal via ear speculum. This will be confirmed on the patient allocation sheet found in the randomisation envelope.

For the postoperative dose group, a new bottle of ciprofloxacin otic drops will be opened in theatre and 5 drops will be placed into the ear canal by the OR nurse through the ear speculum. The same bottle will then have the patient's identity label attached with dosage instructions and given to the patient on discharge. This will be recorded in the operative notes, and a formal prescription for ciprofloxacin otic drops will also be given.

The pharmacist (or the investigator's designee) will maintain accurate records of the receipt of all study medication, including dates of receipt. In addition, accurate records will be kept regarding when and how much study medication is dispensed and used by each patient in the study. Reasons for departure from the expected dispensing regimen will be recorded. At the end of the study, there will be final reconciliation of study drug received, dispensed, consumed and returned. Any discrepancies will be investigated, resolved and documented by the study team. Unused study drug will be destroyed in compliance with applicable regulations.

### 7.2.5 Measurement of participant compliance

Participants in the multi dose group will be required to self-administer medication at home. Participant compliance will be monitored by the use of a post-operative patient dairy to document the time and date of doses, as well as asking the patients to bring unfinished and empty bottles of ciprofloxacin otic drops to the 6 week postoperative review appointment. Participants who have missed more than two consecutive doses or 4 total doses in total will be considered 'significantly non-compliant'. These participants will be noted and analysed separately in the final analysis.

### 7.2.6 Excluded medications and treatments

During the study period, the following medication are restricted:

- systemic antibiotics such as "Amoxicillin, Augmentin, Keflex, Cipro, Erythromycin"
- topical antibiotic ear drops such as "Ciloxan, Ciproxin HC, Sofradex, Kenacomb otic"
- systemic corticosteroids such as "prednisolone, cortisone, dexamethasone"
- non-steroidal anti-inflammatory drugs (NSAIDs) such as "aspirin, Nurofen, Celebrex, Meloxicam, Indocid"

The use of these medications will result in withdrawal of the patient from the study.

## 8 RANDOMISATION AND BLINDING

A researcher not directly involved in the analysis of the study results will prepare the randomisation schedule using sequentially numbered identical brown paper envelopes containing the patient's group allocations in a 1:1:1 ratio.

### 8.1 Concealment mechanism

The envelopes will be placed in a secure location in the operating theatre and opened at the time of surgery. The envelope number will be recorded and will be used as the patient's participant number. The envelope number will also be recorded on the allocation sheet. The allocation sheet will then be collected at the end of each week and stored in a secure archive in the ENT department and recorded electronically on a secure encrypted spreadsheet within the department servers.

Upon review, the patients allocated to either single-dose or control groups will be blinded of their treatment allocation, however the multi-dose group will not be blinded of their treatment allocation. The reviewers will be blinded of the treatment allocation for all groups.

### 8.2 Breaking of the Study Blind

#### 8.2.1 On study

The allocation for individual participant may be unblinded in emergency situations, where the Investigator decides a participant cannot be adequately treated without knowing the identity of their treatment allocation. To break the blind the Investigator will contact the randomisation personnel who will search for the participant number in the allocation spreadsheet. If any unblinding occurs, the time, date, participant number and reason for opening must be documented.

#### 8.2.2 On completion of the study

The trial allocation spreadsheet will be available once all data collected have been entered into the study database for every participant and the database has been finalised, except in the case of an emergency, as detailed above.

## 9 STUDY VISITS AND PROCEDURES

### 9.1 Schedule of assessments

	STUDY PERIOD					
	Enrolment	Surgery	Post-allocation			
TIME POINT**	-t <sub>14-28</sub>	0	t <sub>1</sub>	t <sub>5</sub>	t <sub>14</sub>	t <sub>48</sub> / Final Visit
ENROLMENT:						
Eligibility screen	X					

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Informed consent	X					
Demographic data	X					
Allocation	X					
<b>INTERVENTIONS:</b>						
Single Dose		X				
Multi Dose		X	↔			
Control						
<b>ASSESSMENTS:</b>						
Otoscopy and Tympanometry	X					X
OMO-22 Questionnaire	X					X
Audiometry	X					X
Intraoperative Assessment		X				
Patient Diary			↔			

9.2 Summary of assessments

Vital Signs and Physical Examination	The Child's weight, height, temperature and heart rate will be examined a routine vital sign examination. Additionally, a Limited Physical Examination will be performed during screening which will include an assessment of General Appearance and an examination of your head, eyes, ears, nose and your throat.
Otoscopic exam and tympanometry	Visual inspection of the tympanic membrane with an otoscope and measurement of tympanic membrane movement via a tympanometer. Ventilation tube obstruction and otorrhoea will be assessed visually. Tympanometry will describe whether the ventilation tube is equalising the pressure between the middle and outer ear.

Otitis Media Outcome-22 (OMO-22)	22 item disease specific validated questionnaire based on a 7-point Likert scale with associated demographic questions. (16)
Audiometry	Visual response or pure tone audiometry testing to assess degree of hearing impairment conducted by a blinded audiologist.
Intraoperative Assessment	7 item questionnaire relating to intraoperative factors.
Patient diary	Post-operative patient reported diary documenting presence of otorrhoea in the immediate post-operative period (2 weeks).

### 9.3 Screening/Baseline (Day -28 to -14)

- Obtain and document consent from potential participant.
- Review medical history to determine eligibility based on inclusion/exclusion criteria.
- Review medications history to determine eligibility based on inclusion/exclusion criteria.
- Perform medical examinations needed to determine eligibility.
- Perform otoscopy and tympanometry as part of standard care
- Complete OMO-22 Questionnaire
- Perform Audiometry as part of standard care

### 9.4 Surgery (Day 0)

- Middle Ear Ventilation Tube placement surgery as part of standard care
- Intraoperative assessment form filled out by surgeon at end of the case
- Patients will receive a discharge pack which includes patient diary.
- Provide information regarding water precautions and safety netting

### 9.5 Post-operative review visit (Day 48)

- Perform otoscopy and tympanometry as part of standard care
- Complete second OMO-22 Questionnaire
- Perform Audiometry as part of standard care
- Review and submission of patient diary
- Provide final instructions to participant {e.g., follow-up of ongoing adverse events, oral hygiene instructions}

### 9.6 Withdrawal visit

If a participant withdraws early or investigator terminates participation, all assessments will be performed according to standard care. The participant will also be asked to complete the OMO-22 Questionnaire and submit their patient diary.

### 9.7 Unscheduled review visit

Participants will be instructed to contact the investigator to arrange a review visit if they have signs of continuing ear infection, discharge or ear pain.



## 9.8 Participant Withdrawal

### 9.8.1 Reasons for withdrawal

The investigator may withdraw a patient from the study treatment and follow-up procedures if the patient:

- Is in violation of the protocol;
- Experiences a serious or intolerable adverse event
- Develops, during the course of the study, symptoms or conditions listed in the exclusion criteria
- Requires a medication that is prohibited by the protocol
- Requires early discontinuation for any reason

The investigator will also withdraw all participants from the study treatment if the study is terminated. Patients are free to withdraw from the study at any time upon their request or the request of their legally acceptable representative. Withdrawing from the study will not affect their access to standard treatment or their relationship with the hospital and affiliated health care professionals.

### 9.8.2 Handling of withdrawals and losses to follow-up

When a patient withdraws from the study, the reasons for withdrawal shall be recorded by the investigator on the relevant page of the CRF. Whenever possible, all patients who withdraw from the study prematurely will continue to undergo scheduled visits for study assessments (follow-up). Patients who fail to return for study assessments will be contacted by the research team in an attempt to have them comply with the protocol. This will be in the form of two telephone calls and a registered letter.

## 10 OUTCOMES

### 10.1 Primary outcome

The primary outcome assessed is the presence of ventilation tube obstruction at 6 weeks as assessed on visual otoscopic examination and tympanometry. This will be conducted by a surgeon in training who is blinded from the patient's group allocation. Ventilation tube obstruction will be recorded if a plug is visible or if a flat type B tympanogram is found in the presence of symptoms of ventilation tube obstruction, i.e. poor hearing, recurrence of middle ear effusion, fullness in the ear.

### 10.2 Secondary outcomes

The secondary outcomes measured are list below:

- Presence of ventilation tube otorrhoea at 2 weeks and 6 weeks. Patient report of otorrhoea in two weeks postoperatively, recorded in patient diary. Otoscopy examination at 6 weeks for presence of otorrhoea by a surgeon in training who is blinded from the patient's group allocation.
- Difference in disease-specific quality of life measure (OMO-22) at baseline visit, 2-weeks postoperatively and 6-week postoperative visit.
- Difference in audiometry results (Visual Response Audiometry or Pure Tone Audiometry whichever appropriate for child) at baseline visit and 6-week postoperative visit.
- Correlation between intraoperative factors (bleeding during surgery, presence and type of middle ear effusion, difficulty of tube insertion) and risk of ventilation tube obstruction and otorrhoea.

- Cost-effectiveness analysis of all groups. Analysed in terms of cost to patients and cost to hospital to prevent cases of ventilation tube obstruction and otorrhoea. Costs will be extrapolated from medication prices from the supplier used by the hospital.

## 11 ADVERSE EVENTS AND RISKS

### 11.1 Definitions

#### Unanticipated Problems:

Unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, and (b) the characteristics of the participant population being studied;
- related or possibly related to participation in the research; and
- suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognised.

Adverse Event (AE): Any untoward medical occurrence in a patient enrolled into this study regardless of its causal relationship to study treatment.

#### Serious Adverse Event (SAE)

Adverse events are classified as serious or non-serious.

An SAE is defined as any AE that:

- results in death; or
- is immediately life threatening; or
- requires inpatient hospitalisation; or
- requires prolongation of existing hospitalisation; or
- results in persistent or significant disability/incapacity; or
- is a congenital anomaly/birth defect.

Important medical events will be considered an SAE when, based upon appropriate medical judgement, they may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

#### Suspected Unexpected Serious Adverse Reaction (SUSAR):

A SUSAR is any SAE that is both suspected to be related to the study treatment and is unexpected (i.e. not consistent with applicable product information).

### 11.2 Assessment and documentation of adverse events

For the purposes of this study the investigator is responsible for recording all Adverse Events, regardless of their relationship to study drug, with the following exceptions:

- Conditions that are present at screening and do not deteriorate will not be considered adverse events.
- Abnormal laboratory values will not be considered adverse events unless deemed clinically significant by the investigator and documented as such.

The description of each AE on the CRF will include:

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**Study Name:** PreVenT-O

**HREC Number:** HREC/18/MonH/182

**Version & date:** version 1.1, dated 11/4/2018

- A description of the AE;
- The onset date, duration, date of resolution;
- Severity (mild, moderate or severe);
- Seriousness (i.e. is it an SAE?);
- Any action taken, (e.g. treatment, follow-up tests);
- The outcome (recovery, death, continuing, worsening);
- The likelihood of the relationship of the AE to the study treatment (Unrelated, Possible, Probable, Definite).

The severity and relationship of an AE will be assessed as per appendix X. The seriousness of an AE will be assessed by an investigator according to the definition in section 9.1, with the following exception:

- Hospitalisation due to progression of disease will not be considered an SAE for the purposes of this study.

Changes in the severity of an AE will be reported. AEs characterised as intermittent will be documented for each episode. All AEs will be followed to adequate resolution, where possible.

### 11.3 Eliciting adverse event information

Adverse events will be recorded from the time the patient signs the informed consent form until 4 weeks after the last dose of study medication. Patients will be instructed to call the study investigator if an adverse event occurs. At every study visit patients will be asked “How have you felt since your last visit?” in order to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalised, had any accidents, used any new medication or changed concomitant medication regimens. In addition, AEs will be documented from physical examination findings, clinically significant lab results or other documents (including patient diaries and correspondence from their primary care physician) that are relevant to patient safety.

### 11.4 Serious adverse event reporting

#### 11.4.1 SAES

Any SAE occurring in a study participant will be reported to the HREC and the Pharmacy within 24-72 hours of occurrence, in accordance with the safety reporting policy of the HREC. The HREC safety reporting form will be completed, signed and submitted by an investigator. This form will also be copied to the Pharmacy.

#### 11.4.2 SUSARS

All SUSARs occurring in a study participant will be reported to the Experimental Drugs Section, Drug Safety and Evaluation Branch of the TGA in an expedited fashion (i.e. within 15 calendar days of first knowledge), or for fatal or life threatening events, an initial or full report within 7 calendar days and a follow-up report if necessary within the 15 calendar day timeframe.

An investigator will complete, sign and submit the SUSAR report.

## 12 DATA MANAGEMENT

### 12.1 Data Collection

The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure

accurate interpretation of data. The investigators will maintain adequate case histories of study participants, including accurate case report forms (CRFs), and source documentation.

#### 12.1.1 Source Data

All physical source data will be scanned into the patient's respective digital data record. The physical documents will then be disposed of in a confidential waste bin.

These physical source documents include:

- Signed PICF forms
- OMO-22 Questionnaires
- Patient assessment forms (preoperative, intraoperative, postoperative)
- Patient post-operative diaries
- Audiometry/Tympanometry results

#### 12.1.2 Data Capture Methods

Physical questionnaires will be used to collect data. They will be collected at the end of each day by the investigator and stored in a locked cabinet in the ENT department until the end of the week where data will be scanned into a secured Monash Health server. The physical questionnaires will then be disposed and destroyed according to Monash Health protocol.

Data will be collected in a non-identifiable format. Names and other identifiable information will be omitted, however patient UR numbers will be collected. Otherwise the data we are collecting mainly revolves around clinical observations, and not personal information. We are not aiming to collect any information related to a child's past medical history, family history, or social history, unless it is specifically related to our exclusionary criteria.

### 12.2 Data Storage

Whilst data is collected and collated, patients to be recorded according to their re-identifiable hospital-based unit record (UR) number. This way, information can be updated and cross-examined by the research team.

From the analysis phase and onwards, all information that may identify a patient will be removed, including UR numbers. Patients will be reassigned research-specific identification numbers (e.g. patient 1, 2, 3...). Patients will be analysed purely based upon clinical data relevant to the trial. Any publications arising from our research will only include relevant clinical data, tables and graphs, cleared of any information that could identify our participants

Data will be stored on secure servers hosted by Monash Health. Only the research team will have access to identifiable data. Deidentified data may be made accessible to participating members of the department of ENT - Head and Neck Surgery.

Identifiable data will be destroyed as per Monash Health protocol. Deidentified data will remain archived on Monash servers as evidence of our research.

### 12.3 Record Retention

All data relating to the study will be kept securely by Monash Health within its patient records database for at least 15 years after the completion of a clinical trial, or until the 25<sup>th</sup> birthday of the youngest participant, whichever is later, in accordance with the requirements of the Therapeutic Goods Administration and Health Privacy Principals. Only the chief investigator will have access to the stored data. Standard archiving procedures apply after the retention period expires.

## 13 STUDY OVERSIGHT

### 13.1 Governance structure

Governance will be provided by the Chief Investigator.

### 13.2 Quality Control and Quality Assurance

Staff training will be provided in trial operation such as obtaining allocation, standardised tests and procedures. Calibration exercises of intraoperative and review assessments will be conducted with staff prior to the start of the trial.

## 14 STATISTICAL METHODS

### 14.1 Sample Size Estimation

The sample size and statistical power analysis were calculated using SPSS Statistics Software (Version 24 Windows).

For the primary outcome measure of Ventilation Tube Obstruction. To achieve a statistical power of 80% and Alpha of 0.05, assuming an incidence of 11% for the control group and 4% for the treatment group, 221 participants will be required for each arm. However, if we were to analyse results based on by-ear analysis, this will mean that only 111 participants are required for each arm. Assuming a drop-out rate of 7.5%, 120 participants will be required for each arm to prove statistical significance between the treatment arms and control.

### 14.2 Statistical Analysis Plan

The primary outcome will be the proportion of ventilation tube otorrhoea in each of the three groups. We will use the one-tailed Fisher's exact test to calculate a p-value for each of the following pairings Control vs Single Dose, Control vs Multi Dose, Single Dose vs Multi Dose. The same will be conducted for the secondary outcome of ventilation tube otorrhoea.

For the secondary outcome of quality of life impact, the difference in OMO-22 scores in the 6-week postoperative visit and baseline will be measured and compared using the Student's T-test. Similarly the mean difference in audiometry results in the postoperative visit and baseline will be measured for each group and compared using the student's T-test.

For the correlation between intraoperative factors and outcomes, the individual factors will be assessed using chi-square analysis to determine if statistical relationships exist between the presence of factors and the outcomes of ventilation tube obstruction and otorrhoea.

#### 14.2.1 Population to be analysed

Intention to treat (ITT) population will be used for data analysis.

#### 14.2.2 Methods of analysis

A statistician will be employed to assist with data analysis.

#### 14.3 Interim Analyses

An interim analysis will be conducted after 150 participants have been recruited and undergone the trial procedures. The results of the analysis will be used as part of associate investigator, Chenkan Wang's research thesis for his BMedSc(Hons) degree. These interim results will be used by the lead investigator to decide whether the trial will continue or terminate.

### 15 ETHICS AND DISSEMINATION

#### 15.1 Research Ethics Approval

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the human research ethics committee (HREC). A letter of protocol approval by HREC will be obtained prior to the commencement of the study, as well as approval for other study documents participant to HREC review.

#### 15.2 Modifications to the protocol

This study will be conducted in compliance with the current version of the protocol. Any change to the protocol document or Informed Consent Form that affects the scientific intent, study design, patient safety, or may affect a participants willingness to continue participation in the study is considered an amendment, and therefore will be written and filed as an amendment to this protocol and/or informed consent form. All such amendments will be submitted to the HREC, for approval prior to becoming effective.

#### 15.3 Protocol Deviations

All protocol deviations must be recorded in the patient record (source document) and on the CRF and must be reported to the PI. Protocol deviations will be assessed for significance by the Principal Investigator. Those deviations deemed to have a potential impact on the integrity of the study results, patient safety or the ethical acceptability of the trial will be reported to the HREC in a timely manner. Where deviations to the protocol identify issues for protocol review, the protocol will be amended as per section 12.3.

#### 15.4 Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators and research staff. This confidentiality covers the clinical information relating to participating participants. The study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorised third party. No evaluation forms, reports and other records will leave the site. All data collected will be in the form of re-identifiable data in the form of a UR number to maintain participant confidentiality. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by HREC.

#### 15.5 Participant Reimbursement

Participation in the trial is voluntary and participants will not be reimbursed for their participation in the trial or costs that fall under standard care. Costs of medications in the treatment groups will be reimbursed.

#### 15.6 Financial Disclosure and Conflicts of Interest

There are no financial or competing interests to declare from any of the investigators.

#### 15.7 Dissemination and translation plan

Results of the study will be presented at national and international conferences and published in peer-reviewed journals. All publications and presentations will be authorised by the chief investigator.

### 16 REFERENCES

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## 17 APPENDICES

### 17.1 Informed consent materials

Please find attached in separate PICF document.

### 17.2 Causality and Assessment of Severity – Adverse Events

The severity of an Adverse Event will be assessed as follows:

- **Mild:** Events that require minimal or no treatment and do not interfere with the patient’s daily activities.
- **Moderate:** Events that cause sufficient discomfort to interfere with daily activity and/or require a simple dose of medication.
- **Severe:** Events that prevent usual daily activity or require complex treatment.

The relationship of the event to the study drug will be assessed as follows:

- **Unrelated:** There is no association between the study drug and the reported event. AEs in this category do not have a reasonable temporal relationship to exposure to the test product, or can be explained by a commonly occurring alternative aetiology.
- **Possible:** The event could have caused or contributed to the AE. AEs in this category follow a reasonable temporal sequence from the time of exposure to the test product and/or follow a known response pattern to the test article, but could also have been produced by other factors.
- **Probable:** The association of the event with the study medication seems likely. AEs in this category follow a reasonable temporal sequence from the time of exposure to the test product and are consistent with the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgement based on the investigators clinical experience.
- **Definite:** The AE is a consequence of administration of the test product. AEs in the category cannot be explained by concurrent illness, progression of disease state or concurrent medication reaction. Such events may be widely documented as having an association with the test product or that they occur after rechallenge.