



Clinical Trial:
Surgery for the Treatment of Otitis Media
in Indigenous Children.

PROTOCOL
Medical V surgical sub-study
NT & WA

Co-ordinating Site: Dept of Otolaryngology
Royal Victorian Eye and Ear Hospital
32 Gisborne St
East Melbourne VIC 3002

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This medical sub-study protocol is designed to be conducted concurrently
with the Protocol for the Clinical Trial:

“Surgery for the Treatment of Otitis Media in Indigenous Children
SURGICAL SUB-STUDY”
dated 25th March 2013
and should be attached to it for full explanation.

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Key Roles & Responsibilities:

Principal Investigators:

- Professor Stephen O'Leary / Royal Victorian Eye & Ear Hospital, Melbourne
- Prof Harvey Coates / Princess Margaret Hospital for Children, Perth
- Assoc Prof Peter Morris / Menzies School of Health Research, Darwin
- Assoc Prof Kelvin Kong / John Hunter Hospital, Newcastle
- Assoc Prof Chris Perry / Brisbane
- Ms Adrienne Kirby / Statistician, Sydney
- Dr Hemi Patel, Menzies School of Health Research, Darwin

Associate Investigators:

- A/Prof Paul Walker NSW
- A Prof Garrett Hunter NT
- A/Prof Simon Carney SA
- Brooke Paisley, Audiologist
- Judith Boswell, Audiologist

List of Abbreviations & Definitions

AE	Adverse Event
AHW	Aboriginal Health Worker
AMSANT	Australian Medical Services Alliance of the Northern Territory
AOM	Acute Otitis Media
CI	Chief Investigator
CRF	Clinical Research Forms
DSMC	Data and Safety Monitoring Committee
ENT	Ear, Nose & Throat
GCP	Good Clinical Practice
HREC	Human Research Ethics Committee
IRB	Indigenous Review Board
MA	Myringotomy and adenoidectomy
OM	Otitis Media
OME	Otitis Media with Effusion
RVE&EH	Royal Victorian Eye & Ear Hospital, Melbourne
SAE	Serious Adverse Event
SOPs	Standard Operating Procedure
rAOM	Recurrent Acute Otitis Media
TM	Tympanic Membrane
VT	Ventilation Tubes
VTA	Ventilation Tubes and Adenoidectomy

Definition:

The term “remote children” in the context of this proposal refers to Indigenous children living in remote communities in desert and tropical regions of Australia.

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1. Background Information & Scientific Rationale

This medical sub-study protocol is designed to be conducted concurrently with the Protocol Clinical Trial: "Surgery for the Treatment of Otitis Media in Indigenous Children" dated 25th March 2013 and should be attached to it for full explanation.

Microbiology In the concurrent Surgery V surgery study, the saliva and serum samples are being collected from all children during the time they are under general anaesthetic. In this medical V surgical sub-study the serum samples will only be taken from participants in the surgical arms of the study to minimize stress and discomfort for the children.

Samples from Surgical participants within this sub-study will be the same for both studies ie:

- **Middle ear fluid**
- **Adenoidal tissue**
- **Saliva** will be collected at surgery and at 12 months to determine the mucosal immune response at the time of surgery and any modification to this response following the surgical removal of the adenoids.
- **Blood** (8mls) will be collected whilst the children are under general anaesthesia.

All participants (medical & surgical) will have:

- **Nasal swab and saliva** samples taken at baseline and again at 12 months.

All specimens will be stored at -70°C and cultured in batches by laboratory staff unaware of the allocation status. Standard methods will be used for culturing, quantification of bacterial load and sensitivity testing of respiratory pathogens (Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis).

For ear discharge specimens, we will also use standard methods for identifying common chronic suppurative otitis media pathogens.

A second sample of adenoid tissue will be stored in Ethanol/PBS at -20degrees.

Hypothesis

For children living in remote areas of Australia:

That adenoidectomy when combined with myringotomy and suction clearance of the middle ear effusion or myringotomy and ventilation tubes will reduce the prevalence of chronic otitis media with effusion (OME), compared with medical treatment.(medical sub-study)

2. Outcome measures

The primary outcome from this study will be control of otitis media.

Control is defined as either A or B below:

A. Bilateral:

- aerated middle ears, and
- absent or infrequent aural discharge in both ears, and
- intact tympanic membranes or drum(s) with a grommet present.

B. Control of otitis media and a dry contralateral ear (irrespective of whether the middle ear is aerated or not).

Note that the presence of bilateral dry perforations without a grommet will be deemed as a treatment failure, as will failure to meet any of the other criteria outlined above.

Aural discharge will be assessed and defined in the following manner. The accuracy of these data will be improved by access to all the clinical records for each child and by parental report. At the end of 12 months, aural discharge will be categorized as either:

- Absent or infrequent (less than three episodes of discharge over 12 months) and no discharge present at the 12 month follow up.
- Recurrent (three or more episodes of discharge) or persistent or discharge present at the 12 month follow up.

The secondary outcome measure will be hearing thresholds. Hearing will be assessed by pure tone audiometry, which is why the minimum age for inclusion in the study is 3 years. The audiometry will be assessed at the 12 month reviews, and categorized as,

- Normal: a PTA is <16 dB in a sound-proofed room and < 25 dB in non sound-proofed conditions.
- Hearing loss, or impairment, when the PTA exceeds the normal values.

Expected outcomes

The main effect of the surgical interventions is expected to be a reduction in the presence of bilateral OME at 12 months by 50%¹⁷. Hearing is expected to improve. Data from other populations reveal that hearing improves following the placement of ventilation tubes³³ or following MA³³. Rates of aural discharge are predicted to increase for VTA and remain minimal for MA, but could vary considerably across different communities within the same region. It has been reported that 37% of ventilation tubes discharge chronically in the tropics²². Accurate data are not available for the desert regions, but the rates of chronic discharge are thought to be about half those in the tropical regions, (nominally 18%).

Secondary outcome: Hearing impairment over 0.5, 1, 2, 4 kHz

An improvement in the rate of hearing loss is defined as an improvement of 10 dB or more in the pure tone average hearing loss (PTA).

The sample size of 100 for each of the medical and surgical arms would have more than 90% power to detect a 30-50% difference between the medical and surgical groups in hearing outcomes in either direction (i.e. with a two-tailed significance), assuming that the rate of hearing resolution falls between 40-60% for surgery, and 10% for medical.

- 1) Ventilation tubes and adenoidectomy vs Myringotomy and adenoidectomy (VTA vs MA) - The study will provide estimates of the rate of hearing loss in each group.

Secondary outcome: Aural discharge

- 1) Superiority - Ventilation tubes and adenoidectomy vs Medical treatment (VTA vs Med).
- 2) Superiority - Ventilation tubes and adenoidectomy vs Myringotomy and adenoidectomy (VTA vs MA).

Approximately 37% of children living in tropical regions and 18% of children living in the desert who have been treated with VTA, will have aural discharge after 12 months. If there are equal numbers of children randomised from both regions, 160 children per arm would have more than 90% power to detect an average reduction of 17% (from 27% to 10%) at 12 months.

Microbiology outcomes and significance:

This study provides a unique opportunity to describe the interactions between the host immune response and the bacteria that cause OM in this extremely high-risk population. We know that these children experience a high disease burden and that this is related to the amount of bacteria carried in the nasopharynx. However we do not know how their immune responses, both systemic (serum) and local/mucosal (saliva and in the middle ear itself) deal with this.

This will be the first study to determine how a high-risk population responds to heavy bacterial loads and to explore the possibility of developing an OM vaccine for this population.

This will also be the first study to describe alterations in the nasopharyngeal bacterial load and local immune responses following removal of the adenoid. These data will aid in understanding the clinical outcomes of the surgical treatment arms and to inform intervention strategies.

Bacterial load estimates of nose swabs will be used to determine whether this measure is able to predict which children are most likely to develop ear discharge and whether adenoidectomy reduces bacterial load in the nasopharynx of Aboriginal children. The analysis of microbiological outcomes will be descriptive. The sample size is sufficient to determine if adenoidectomy is associated with a 15-20% reduction in proportion of children with nasopharyngeal bacterial carriage and a 0.3 standard deviation reduction in the nasopharyngeal bacterial load.

3. Experimental Design Overview

This will be a multi-centre randomised trial (allocation concealed) of the effects of one medical and two surgical interventions in the management of chronic OME with the primary outcome determined by a blinded assessor.

The medical / surgical substudy will require 200 participants and run for 3 years assuming a 33% enrolment of potential participants (approximately 100 in NT & 100 in WA utilizing 6 hospital sites). Initially the randomisation process will be conducted from the community and will allocate the 200 children to Medical or Surgical treatments (1:1).

Children allocated to the medical group will be assigned treatment by the ENT specialist and not be transferred to hospital. Treatment will be documented in the CRF.

Children who are allocated to "surgical" intervention will be transferred to hospital where they will be randomised a second time to either:

- (1) adenoidectomy with ventilation tubes (VTA)
- (2) adenoidectomy with myringotomy only (MA)

The children will be followed up for 12 months following intervention. It is expected that at the end of this period many of the ventilation tubes will have extruded (often within 3-6 months), and that the OME/AOM will likely have recurred if were to do so. The primary outcome measures will be a reduction in the prevalence of OME/AOM (as defined above).

All treatment and follow-up for the surgical participants is identical to the children in the Surgical study.

A medical control arm is essential in this study, for the following reasons:

- i) there are few data demonstrating efficacy of surgery and some hold the opinion that surgery is harmful; and
- ii) no surgery is the reality for most children living in remote communities. The implications of the trial for clinical practice, policy and resource allocation will be profound (irrespective of the outcome).

Statistical considerations

The study is a multi-centre randomised controlled trial with ongoing medical care (e.g. antibiotics, hearing support and watchful waiting) being the control. The total sample size of 200 children is calculated allowing for 20% lost to follow-up in the calculations detailed below. There will be equal allocation to the medical and surgical interventions, Children allocated to the surgical arm will be re-randomised at hospital to either of the surgical arms (1:1, VTA:MA) Interventions

- adenoidectomy with ventilation tubes (VTA)
- adenoidectomy with myringotomy only (MA)
- medical treatment (Med) including antibiotics, assessment for hearing support and watchful waiting with the offer of surgery after 12 months if clinically indicated.

Comparisons for primary outcome

- 1) Superiority - Ventilation tubes and adenoidectomy vs Medical treatment vs (VTA vs Med)
- 2) Superiority - Myringotomy and adenoidectomy vs Medical treatment (MA vs Med)

Power and sample size

Recurrence of bilateral OME

For an overall significance level of 5% to be maintained, the predefined comparison in this medical-vs-surgical sub-study will be compared at the 2.5% significance level. These comparisons are as above. The sample size of 100 per arm would have more than 94% power to detect a reduction of 30%, from a recurrence rate of 90% in the medical care arm to 60% recurrence in either of the surgery groups. The comparisons between the medical group with each of the surgical arms will carry a two-tailed significance level of 1.25% each.

Predefined Subgroup analyses

Analyses will also be carried out for various subgroups which will include:

- Remoteness of living circumstance, i.e. distance from hospital treatment;
- Age: 3-5, 6-10 yrs.

Data Analysis

All results will be analysed on an intention to treat basis. The primary and secondary outcomes of recurrent bilateral OME, aural discharge and presence of hearing impairment will be analysed using both univariate and multivariate logistic regression to compare the three treatment groups.

3. Study Enrollment & withdrawal

Inclusion criteria

- Indigenous children aged 3 - 10 years old living in remote communities
- OME/AOM that has been present for ≥ 3 months and failed medical treatment. The criteria for the diagnosis of glue ear will be the presence of an immobile tympanic membrane on pneumatic otoscopy, supported by an air-bone gap on audiometry and a Type B tympanogram.
- A mild or moderate conductive hearing impairment, defined as a pure-tone average of >20 dB when tested in a sound-proofed room, or >30 dB when tested in non sound-proofed conditions. Approximately 70% of children with OME/AOM are expected to meet this criterion.

Exclusion Criteria

Children with any of the following conditions which may predispose to complications following adenoidectomy:

- Cleft palate
- Submucous cleft palate
- Down Syndrome

- Cranio-facial syndromes
- Generalised immunological diseases
- Bleeding diathesis
- Requirement for concomitant tonsillectomy

Also exclude

- Children requiring treatment of unilateral ear pathology

Recruitment:

Children referred for ENT assessment who have failed initial medical care for their otitis media will be eligible to participate in the study. Recruitment will not be considered until a child is found to be a potential surgical candidate in an ENT clinic or as advised by an ENT surgeon. Randomisation will occur after a decision has been made that surgery is amongst the next treatment possibilities. We aim to recruit 15-20 children per month (~5-8 per centre). Data must be available showing audiometry testing within the previous 6 months.

Randomisation: NT & WA (3 arms)

To minimize the inconvenience and cost of transferring children and carers to hospital and then sending 50% back to their communities with no surgical intervention, children will be recruited in the community. One or two larger communities in each hospital catchment area will be approached for a letter of support from the local elders.

After consent, all children will be randomly allocated by IVRS to receive either medical or surgical intervention (1;1). The children who travel to hospital for surgery will then be re-randomized into either of the 2 surgical interventions, with equal allocation.

Allocation will be stratified by hospital site and age (3-5, 6-10yrs.). Children will be allocated via a central randomisation service (IVRS system) provided by NHMRC Clinical Trials Centre. The random allocation sequence will be determined by minimisation. The allocation sequence will be concealed from the investigators and research staff at all times.

Follow-up and Blinding:

Follow up will take place at 12 months in the community by clinically-trained researchers competent in otoscopy and audiological assessment. The outcome assessors will be blinded to the treatment group. Tympanometry and video-otoscopy will be used to validate the final outcome assessment.

Reasons for withdrawal

The local clinician or Investigator has the right to withdraw a participant at any time. It is recommended that a clinician removes a child from the study if he/she feels continuation would be harmful to the child or if the study is cancelled.

The parent may withdraw the child from the trial at any time without causing prejudice to their treatment by the clinic and doctor.

Handling of withdrawals

All withdrawals will be recorded as clinician decision or parental withdrawal. A request will be made to collect outcome data as originally planned. Refusal to allow further data collection will be documented for each study outcome measure. Children lost to follow-up because of relocation will not be considered withdrawals. Where withdrawal or loss to follow-up precludes the collection of primary outcome data, these cases will not be included in the analysis.

2. Clinical Evaluations

At the screening assessment, the following will be used to confirm eligibility:

- Review of clinical medical records for Otitis Media history
- Clinical assessment (when available)
 - Audiometry
 - Tympanometry

- Video-otoscope pictures of tympanic membrane
- Other health issues

The following information will be recorded for IVRS:

- Date of birth
- Sex
- Hospital

All clinical assessments will be made by trained ear health officers or suitably qualified research staff.

At Randomisation the following information will be obtained:

- Audiometry,
- Tympanometry
- Videoscope pictures of the eardrums
- Nasal & saliva swabs

For surgical interventions the following samples will be taken:

- Blood (8mls)
- Adenoid tissue if available
- Middle ear discharge if available
- Record details of procedure
 - VTA or MA
 - Type of samples collected
 - Discharge medications
 - Post op events (haemorrhage / fever / excessive pain etc)

Monthly Phone calls for 11 months

If the family has a mobile phone and is willing to be contacted monthly, the call will be made directly to the person at the details provided. This permission for follow-up access to information is part of the signed, informed consent document.

If there is no phone contact, Trial Coordinators will make monthly phone calls or emails to Remote Health staff in communities where children in the trial were last known to be living. Where a community health database is in operation, this may be accessed.

The caller will ask:

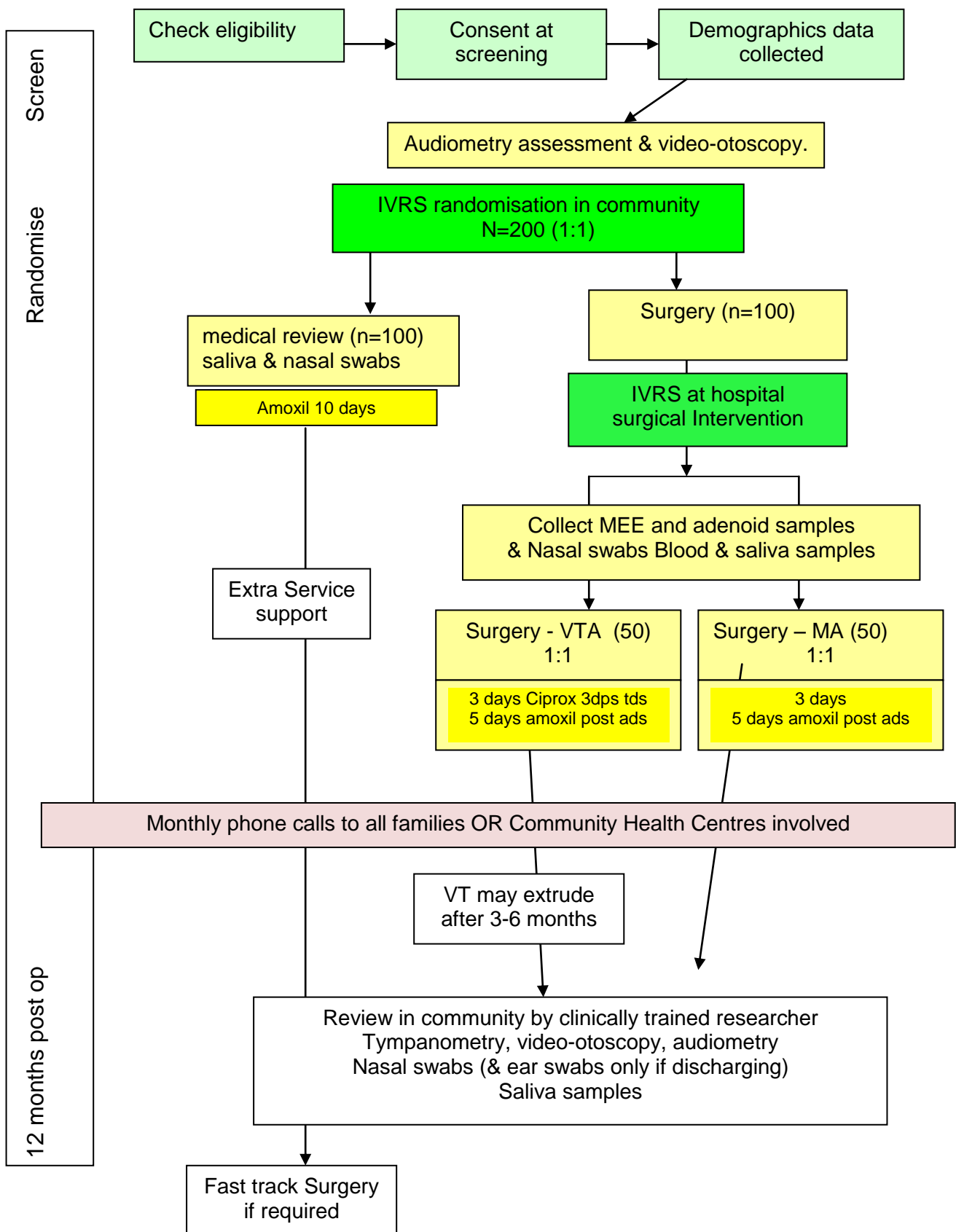
- if the child is known to be living in the area?
- If not, where have they moved to?
- If they have attended clinic for any reason? (if so, why?)
- Were they observed to have discharging ears?

These calls will provide a potential link to children who may otherwise be lost to follow-up and also provide data for Adverse Event tracking and regular review of those in the medical intervention group.

Final Contact

The outcome assessor will visit the child in his/ her community and complete the following tasks:

- Audiometry,
- Tympanometry
- Videoscope pictures of eardrums
- Nasal & saliva swabs
- Aural swabs if discharge present
- Review of clinic records
- Record any AEs still outstanding or not previously noted
- These results will determine if further treatment / referral is required.



6. Safety Assessments

An Adverse Event (AE) is any adverse change in health that occurs in a person who participates in a clinical trial while the patient is receiving the treatment (study medication, application of the study device, etc.) or within a previously specified period of time after the treatment has been completed. In this trial, the observation period is for 12 months following intervention.

Serious Adverse Event (SAE) is an unanticipated problem involving “risk” to subjects that ultimately results in harm to the subject (impacts on subjects morbidity and mortality) or others. SAE reports must be filed with the Project Manager and the local Ethics Committee when any of the following happens to a subject on a study:

1. Death
2. Unanticipated “risk” or event requiring life-saving treatment, hospitalization or prolongation of existing hospital stay
3. Any suspicious findings that participants, investigators or clinicians may have relationship to the study

Sample Management

See the Microbiology SOP and related appendix for guidelines for the use and safe management of dry nitrogen shippers.

Sample containers will be taken to the field by the research team. The swab collection vials need to be kept cool at all times. Once the specimens have been collected as per SOP instructions they need to be frozen and remain so for transportation. The use of a dry nitrogen shipper will mean specimens can be kept frozen until returned to Menzies Laboratory, stored and transported according to the Manual provided by Menzies Laboratories in Darwin.

Where impractical or where a shipper is unavailable, specimens may be frozen in a -80C fridge and sent in a batch to Menzies using a commercial courier. If freezing is a problem, or there is a possibility of swabs thawing during transport, specimens may be transported chilled as long as they reach the lab within 24 hours of collection. Immediate freezing is preferable. Please ensure that specimens are frozen upright (so the swab tip is immersed). On arrival at Menzies, the samples will be kept in -70°C freezers for long term storage.

Treatment Protocols

All children will have preoperative audiometry and tympanometry and clinical assessment to rule out other conditions which may be associated with complications. These include cleft palate, submucous cleft palate, Down Syndrome, cranio-facial syndromes, generalized immunologic diseases and bleedings diathesis.

Adenoidectomy will be performed under direct vision utilizing a suction diathermy or curette technique followed by five days of the oral antibiotic, amoxycillin (or cotrimoxazole if allergic to penicillin) to reduce the risk of postoperative infection, bleeding and halitosis. Adenoidal tissue will be biopsied for culture and histopathological analysis.

Ventilation tube insertion will be of a standardized tube (Shephard’s) in the anterior inferior segment of the tympanic membrane after aspiration of the middle ear fluid. All children having ventilation tubes will be prescribed post-operative Ciprofloxacin ear

drops (Ciloxan ®) with three drops three times a day for three days to reduce post operative otorrhoea and blockage of the tube.

Myringotomy alone will be a small radial incision to the anterior inferior segment of the tympanic membrane with suction of middle ear fluid.

The parents/carers will be counselled to seek medical attention if there are signs of secondary haemorrhage from the adenoid region. Paracetamol or similar analgesia (rather than non-steroidal medications) will be prescribed post operatively.

Children allocated to the medical control arm will have already failed “standard medical care”. These children will receive additional specialist attention. This will include advice (written and verbal information with an interpreter if required) about the management of hearing and effective communication strategies, further antibiotic treatment (10 day course of amoxicillin) and assessment for additional hearing support as appropriate.

Progress after randomisation for all children will be monitored by the monthly contacts with the child’s local community Health Centre.

Complications

The mortality of the type of paediatric anaesthesia required for VT or adenoidectomy is estimated to be less than ~1:50,000³⁵. It should be noted that enrolment for this study will be made only for potential surgical candidates, so this risk will already have been accepted prior to recruitment into this trial.

And although there is systematic evidence to conclude that with adenoidectomy there is an overall benefit over harm for duration of OME¹⁷, there is added complexity from this procedure. The most significant risk is of post-operative bleeding, but the rate is very low at 0.2-0.5%^{19,20}. This occurs most often in the first few hours after the procedure when the child is still in hospital. Transient velopharyngeal incompetence has an incidence of 2%³⁶. Other potential risks such as nasopharyngeal stenosis and persistent velopharyngeal insufficiency are rarely seen, and can be minimized with appropriate patient selection and surgical technique¹⁷.

Ventilation tube insertion also carries with it a small but significant number of potentially adverse outcomes. These are principally related to post-operative (early and late) otorrhoea. The reason for considering the MA group in this study, and for having aural discharge as a secondary outcome variable, is to determine whether the prevalence of otorrhoea can be reduced by recommending MA over VTA. Other complications included early extrusion of the tube, retained middle ear tubes (especially with use of tissue spears post operatively), a 2% risk of residual perforation after ventilation tube has extruded, and rarely cholesteatoma (0.5%)³⁷. Tympanosclerosis and focal atrophy may occur, but these have been found not to be of functional significance or effect the hearing³⁷.

In the present study, potential complications will be explained to participants’ carers in culturally appropriate ways. Any complications will be treated medically, recorded and reported to the Trial Management Committee. It is most unlikely that there will be a significant number of adverse events, given that all of the treatment arms are standard clinical practice. All serious adverse events (SAEs) will be reported to the Independent Data Safety and Monitoring Committee.

8. Trial Governance and Management

Institutional review Boards

Victoria – Royal Victorian Eye & Ear Hospital HREC gave approval (27 June 2011).

NT – both Top End and Central Australia

WA – WACHS & WA AHIEC

These review boards operate in accordance with the NHMRC Act of 1992 and the National Statement on Ethical Conduct in Research Involving Humans 1999.

An Independent Data and Safety Monitoring Committee (DSMC) will report to the Reference Group and comprise two ENT specialists, a paediatrician or general practitioner, a statistician and at least one Indigenous representative for participating communities. All members will be independent of the trial. This group will monitor any serious adverse events throughout the study and recruitment. The following outcomes will be reviewed: a. Rates of recurrence of OME, b. the number episodes of aural discharge post-surgery, c. Secondary haemorrhage from the pharynx following adenoidectomy, d. Compliance of clinical attendance for children enrolled in the trial. The Trial Management Committee will report to the Reference Group, and comprise of the CI's and researchers. Its role will be to ensure the scientific integrity of the trial, resolve related issues that arise and monitor the rate of data collection. The trial co-ordinator will report to the Trial Management Committee. Their role will be to liaise with Hospitals, communities and researchers, deal with regulatory matters, manage data quality, maintain the database, organise travel and meetings, the preparation of reports and data summaries for the statisticians at CTC (Sydney) and IDSMC, and have a limited clinical role in data collection. Some of this responsibility may be delegated to the regional researchers, in consultation with those individuals. The regional researchers will be directly responsible for the data collection in their regions, and for building and maintaining an effective working relationship with communities.

9. Informed Consent Process – Medical v Surgical Sub-study

Recruitment will not be considered until a child is found to be a candidate for surgery. The surgeon and an Aboriginal Health worker (acting as interpreter if required) will explain the study using pictorial Patient Information sheets which have been adapted for people with little English and poor literacy. These pages have been developed especially for this study.

Subject Confidentiality

Subject confidentiality is strictly observed by the participating investigators, the research and clinic staff authorized to view their medical records for study purposes. Children's names will be de-identified by study codes on all data used for analysis, and all laboratory specimens.

All information gathered will be kept in locked cupboards and on computers which are password protected.

Study Discontinuation

In the event that the study is prematurely discontinued, every effort will be made to inform communities where children are still enrolled in the trial, if necessary arranging referrals to health services for follow-up.

Future Use of Stored Specimens across both sub-studies

All tissue samples (nasal / aural swabs & adenoid tissue) collected for the trial will be handled according to the wishes of the community & or family and documented on the consent form.

Aboriginal Committees in Qld and WA have expressed concern that the samples may be used for purposes outside the boundaries of the study if wider, unspecified consent is

given. **Therefore all samples will be destroyed at the study end for Qld & WA.** Samples collected in NT are subject to individual parent choice and written consent.

NT parents will have the option of having all specimens (or selected specimens) destroyed after all laboratory testing has been done at the end of the trial or having the specimens kept for further related research on OME. They will not be used for any other study. If, during the course of the trial the researchers find a reason to conduct further tests on these samples not related to OME, the parents will be notified and new consent will be obtained.

10. Issues Relevant to Research in Aboriginal Communities

The conduct of a nation-wide randomized controlled trial involving many different Aboriginal communities and language groups represents a major challenge. The trial will be controlled by a Reference Group with representatives from all stakeholder groups, including the Indigenous communities, health care providers and researchers. The group will be convened by an Indigenous surgeon and researcher (CI Dr Kelvin Kong).

Aboriginal Health Workers will be employed in locally to liaise with parents and communities. The project has written support from the area Aboriginal Health Services as their staff will be contacted to give information re the monthly follow-up.

The medical study requires a letter of support from specific communities in which it will be based.

See surgical protocol for the following information:

Quality Control & Assurance

Reference Group

Independent Data and Safety Monitoring Committee (DSMC)

Data Handling & Record Keeping

Publication Policy

Literature References -

Medical Sub-Study Flow Chart

	Screen Visit	Intervention Day	Monthly Phone calls	Pre term visit	Termination Visit
Informed consent	✓				
Inclusion / Exclusion criteria	✓				
Demographic data	✓				review
Contact IVRS		✓			
2 nd IVRS		Surgical group only			
Medical history	✓		✓		✓
Ear History	✓		✓		✓
Current concom medications	✓	✓	✓		✓
Audiology testing	✓				✓
Tympanometry	✓				✓
Video-otoscope pictures	✓				✓
Microbiology sample collection		✓			✓
Advise Menzes Lab to expect samples		✓			✓
Book World Courier		✓			✓
Transfer samples		✓			✓
Complete eCRF		✓	✓		✓
Parents consent to phone	✓		✓		
Check phone consent page Phone parent or Comm Worker??			✓		
Phone using list of questions			✓		
Adverse events check		✓	✓		✓
Contact community for written consent to visit at 12Months				✓	