

## Low dose of oral corticosteroids in the treatment of painful acute otitis externa (swimmer's ear)

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## **I. Summary, significance and innovation**

Otitis externa is a frequent problem worldwide, especially in the tropics. Since the pain and swelling often makes proper topical treatment difficult some medical practitioners use oral prednisolone as an adjuvant therapy. However, there is yet no scientific evidence supporting this treatment. If the clinical observation made by those doctors already using oral corticosteroids can be proven correct then it might reduce pain and complications in a far greater number of patients. If oral corticosteroids have no beneficial effect, or even harmful effect, then it is important that this information is made public so GPs currently using oral corticosteroids can change. Thus, any of the possible outcomes of this study has the potential of altering current practice.

## **II. Introduction**

Otitis Externa (Swimmer's ear) is an inflammation of the outer ear and ear canal. It is a common problem presenting to General Practitioners particularly in coastal temperate and tropical Australia. Its monthly incidence in US increases during summer season from 0.2% to 1.4% of the population (1). Furthermore, otitis externa is much more common in regular swimmers compared to non-swimmers (2). This indicates that that the climate is of importance. There are no data for annual incidence in Australia. However, in the tropical parts of Australia the annual incidence can be expected to be much higher than 1.4% of the population.

The skin in the external ear canal of a healthy ear has a thin protective coating of cerumen, a mixture of secretions from apocrine and sebaceous glands mixed with desquamated epithelial cells. Interruption or alteration of this protective layer by trauma and /or exposure to moisture may result in inflammation. Many factors such as genetic (shape and size of ear canal, effectiveness of immune system, concomitant dermatological illness), environmental (tropical climate), occupational (hearing protection and / or humid working conditions), recreational (water sports) and personal hygiene (use of ear buds, attempts at cleaning the ear canal with water) facilitate the development of such inflammation. This inflamed skin may secondarily get infected. However, in at least one third of patients an infectious organism cannot be found (3). In the other two thirds it is not always clear if the found organism is causing the signs and symptoms or, if it quietly resides in the ear canal and is found by mistake. However, in severe cases a secondary infection is likely.

Common consequences for the patient of otitis externa are pain, sleep disturbance, temporary loss of hearing, pharmaceutical and consultation expenses, and perhaps loss of income. Initial symptoms at presentation to medical practices range from mild irritation with almost no pain to strongest pain imaginable (4). The average experience is slightly below "very strong pain" (4). The pain is often proportionate to the swelling in the ear canal, which if canal closure occurs also makes the condition very difficult to treat with topical medication. The consequences for society are health costs and loss of productivity. The most common outcome of otitis externa is full recovery after 5-14 days (4).

In rare cases severe damage to the pinna, outer and middle ear may sometimes result in significant hearing loss. In these severe cases infection may also spread to deeper structures such as the inner ear and the brain threatening the patient's life. (5)

The treatment for otitis externa is usually topical and in selected cases oral antibiotics (6, 7). In an Australian study (3) of 201 patients 95% of all patients received topical treatment and 30% oral antibiotics. The typical topical treatment consists of antibiotics and corticosteroids (3). Rosenfeld et al (8) made a systematic review stating that topical corticosteroids alone is of equal effects as topical corticosteroids plus topical antibiotics. Roland et al (9) found that topical treatment with a more powerful topical steroid might be more effective than topical treatment with a less potent topical steroid even if the latter is combined with antibiotics(9-11).

For many years a published “practice tip” of using oral corticosteroids is being used by a small minority of General Practitioners (3, 7, 12). This tip recommends a short course of oral corticosteroids to reduce the swelling and gain pain control and access to the canal for topical medication and cleaning (13). Those General Practitioners perceive that pain relief is faster, often dramatically, and recovery expedited. The oral corticosteroids prednisone or prednisolone is used in doses ranging from 20-75mg daily for 3-5 days.

Corticosteroids reduce the immune response. Hence, corticosteroids given to a patient having a severe infection might put the patient into a worse situation. However, it is shown that corticosteroids can be given safely and with beneficial effect to patients having an ongoing infection of low or moderate virulence. Examples are patients with croup (14) and the sore throat (15-17).

Acute otitis externa is in most cases is an aseptic inflammation, an inflammation simultaneously colonised by bacteria or an infection of low to moderate virulence. In those situations corticosteroids could theoretically be beneficial. Current extensive research shows that a topical steroid is beneficial to patients having otitis externa (11). This is a strong indication that otitis externa rarely is a highly virulent infection and that the risk of using oral corticosteroids within reason is small.

### **III. Study rationale**

To date there does not appear to be one single clinical trial evaluating the effect of oral corticosteroids for patients having otitis externa. Giving oral corticosteroids to patients with otitis externa may be beneficial or harmful. It may be that oral corticosteroids in the lower dose range are beneficial while adding more corticosteroids just add more side effects and risks. If a short course of oral corticosteroids in a low dose (20mg Prednisolone daily) are beneficial then this knowledge needs to be presented and practitioners using a higher dose should be recommended to lower the dose of corticosteroids. If a benefit of oral corticosteroids cannot be proven then physicians currently using it need to be advised that this treatment is of no proven value.

### **IV. Study Objective / Aim**

The objective of the present study is to assess the efficacy of low dose oral prednisolone for four days in addition to conventional therapy in the management of painful acute otitis externa. Primary research questions and data collection aim to comply with the only published validated questionnaire for acute otitis externa(4).

## **A. Primary research questions**

- a) Will oral corticosteroids reduce time (number of days) to resolution of pain?
- b) Will oral corticosteroids reduce the number of “lost hours” in respect of:
  - 1) need for bed rest
  - 2) activity limitation
  - 3) paid work missed
  - 4) need for paid child/elder care
- c) Will oral corticosteroids increase patient satisfaction concerning:
  - 1) burning or stinging feeling post administration of topical treatment
  - 2) itching post administration of topical treatment
  - 3) time to resolution of pain
  - 4) time to resolution of itching
  - 5) time to resolution of swelling
  - 6) time to resolution of discharge

## **B. Secondary research questions**

- a) Will oral steroids reduce:
  - 1) The need for unplanned revisits
  - 2) The need for exclusion due to worsening of symptoms
- b) Will Indigenous patients have the same outcome as Caucasian patients?
- c) Will oral corticosteroids increase patient satisfaction concerning time to resolution of normal activities?

## **V. Patients and Methods**

### **A. Study design**

Randomized controlled clinical trial (RCT) using two unmatched groups.

### **B. Study outline / logistics**

#### **1. Web site**

GPs and pharmacists will be recruited by personal phone calls and visits. A website will be created to assist participating GPs and pharmacists showing example videos of what they need to do. The website is also an introduction in case new GPs and pharmacists would like to participate. Already participating GPs and pharmacists can refer interested colleagues to the website where further contact details are found. Amendments to the ethics committee and TGA will be made in case adding more GPs and pharmacists also means adding a new site.

The website will not be used to recruit patients. However, it will contain some information for patients taken from the patient information sheet (with emphasis on what participating patients

should do in case symptoms get worse) in case patients accidentally find the website. The address to the website is <http://www.otitisexterna.net/>.

## 2. Screening and inclusion of patients

Patients will be screened by GPs (Appendix 1) and included by pharmacists (Appendix 2).

Patients attending their GP who are diagnosed as having an otitis externa are **noted with age and gender on a “GP screening sheet”** (Appendix 3). They are asked by their GP if they accept being evaluated for participation in a study. (*“There is a study going on at James Cook University concerning a new treatment of this type of ear inflammation. Your case may be suitable. May I ask a few questions to see if you fit the inclusion criteria? If you do you will be given more information before deciding to participate.”*) If they do say no the GP does nothing more.

**If they say yes the GPs follow instructions on an “inclusion sheet”** (Appendix 4). **The GP tick the appropriate boxes and note the unique ID number of the “inclusion sheet” on the “GP screening sheet”**. If they do not fulfil the inclusion criteria the GP will retain the inclusion sheet. If they fulfil the inclusion criteria the GP gives the inclusion sheet and any written prescription to the patient and the patient is also given a list with specified pharmacists (Appendix 5) located nearby. These pharmacists will give the patient further written information (Appendix 6), ask for participation and give patients accepting a written consent form to sign (Appendix 7).

The pharmacist will give the patient a “study tablet” being either oral corticosteroids or placebo (determined by randomisation). The patients will be asked to complete a daily diary (Appendix 8) and a satisfaction questionnaire (Appendix 9) later to be sent directly to the research co-ordinator by mail. This will be our only source of information.

Patients will be phoned 1-3 days after inclusion to hear how they are doing and to remind them of the daily diary and questionnaire.

## 3. Folders and pens

All GPs and pharmacists will get a folder with all necessary content. On the front cover will be a short summary of what they are expected to do. A pen will also be distributed with the folder. It will have the address to the website mentioned above and the text “2.5/10 fnqgp research”. 2.5/10 is a reminder that only patients with a pain of at least 2.5cm on a 10 cm long visual analogue scale should be included. Fnqgp is short for Far North Queensland GP research, an informal network of GPs participating in research. The pen will also have the phone number 0407156246 printed on it. This phone number goes to Dr Balch (or another person in the research team).

## C. Study population

### 1. Sample size calculations

All sample size calculations are made two tailed (not assuming that a difference between groups always favour the intervention group). Sample size calculations are based on the primary research questions given above using a validated patient diary and patient satisfaction questionnaire (4).



**a) Sample size calculation for analysis of “Time to resolution of pain”**

In this analysis we use the patient diary to compare days until pain free (VAS 0mm of maximum 100mm) or almost pain free (VAS ≤10mm of maximum 100mm) using log rank test.

Assuming a hazard ratio between intervention and control group of 1.75 (a patient at any given time has a 75% higher probability of being cured at the next time point compared to patients in the other group). Furthermore we assume a power of 0.95 and an alpha of 0.05 and that 15% of data are censored (we lack information on if they got well or not). During these circumstances we would need 99 patients in each group, in total 198 patients. The sample size calculation was done with the software PASS version 11.0.8 (Hintze, J. (2011). PASS 11. NCSS, LLC. Kaysville, Utah, USA. [www.ncss.com](http://www.ncss.com).)

**b) Sample size calculation for analysis of “Lost hours”**

In this analysis we aim to find the sample size needed to find a true effect size close to 0.70 (medium to large effect) with a power of 0.95 and a probability of an alpha error being 0.05. The sample size calculations are based on group comparisons and we use item 16-19 in the patient diary developed and validated by Shikiar et al. (4). This publication yields mean and standard deviation (SD) for the control group. However, in several items it seems unrealistically optimistic to have an effect size of 0.7, mainly due to a rather high SD. In that case we calculated the theoretical effect size of a reasonable improvement by the intervention.

Lost hours per day	Questionnaire item (4)	Primary research question	Statistical method	Estimated effect size	Mean / SD intervention group	Mean / SD control group	Sample size in each group	Total sample size
Bed rest	16	b1	Mann-Whitney	0.68	1.1 / 1.5	2.2 / 3.19	60	120
Activity limitation	17	b2	Mann-Whitney	0.53	0.7 / 0.9	2.79 / 5.5	98	196
Paid work missed	18	b3	Mann-Whitney	0.56	0.44 / 0.5	0.88 / 1.0	89	178
Paid care	19	b4	Mann-Whitney	0.61	2 / 2	3.96 / 4.0*	72	144

\*SD not given by Shikiar et al. We made an assumption.

The above calculation is made on hours per day because that is the information given in Shikiar’s article. After data collection we plan to calculate statistics on total number of hours recorded until well or up to a 10 day period (whichever happens first). However, we find it reasonable to use Shikiar’s data for sample size calculation since they are the only accessible data. In summary a total number of 196 patients would be enough to achieve statistical power in all items. This sample size calculation was done in the statistical software G\*Power version 3.1.3 (18, 19).

**c) Sample size calculation for analysis of “Satisfaction with symptom resolution”**

In this analysis we aim to find the sample size needed to find a true effect size ≥ 0.70 (medium to large effect) with a power of 0.95 and a probability of an alpha error being 0.05. The sample size calculations are based on group comparison and we use item 10-16 in the satisfaction with symptom resolution questionnaire developed and validated by Shikiar et al. (4). This publication yields mean



and standard deviation (SD) for the control group. We assume that the intervention group will have the same SD as the control group. We use the estimated effect size of 0.7 except in those cases where mean for a question in the intervention group would need to exceed 4.5. The theoretical maximum response on a single question is 5.0 but we do not expect to supersede a mean in the intervention group higher than 4.5. In these cases we use the effect size that would be the consequence if we limit the response in the intervention group to be no higher than 4.5. The effect size will consequently be lower than 0.70 demanding a higher sample size.

Category	Item	Primary research question	Statistical method	Estimated effect size	Intervention group (mean)	SD in each group	Control group (mean)	Sample size in each group	Total sample size
Side effects	10	c1	Mann-Whitney	0.70	4.26	1.13	3.47	57	114
Side effects	11	c2	Mann-Whitney	0.70	4.41	1.19	3.58	57	114
Relief of symptoms	12	c3	Mann-Whitney	0.70	4.47	1.06	3.73	57	114
Relief of symptoms	13	c4	Mann-Whitney	0.70	4.49	1.03	3.77	57	114
Relief of symptoms	14	c5	Mann-Whitney	0.54	4.50	1.23	3.83	93	186
Relief of symptoms	15	c6	Mann-Whitney	0.71	4.47	0.95	3.80	56	112
Relief of symptoms	16		Mann-Whitney	0.33	4.5	1.03	4.16	251	502

In summary a total number of 114 patients would be enough to achieve statistical power in most items. A total of 186 would also achieve statistical power in item 14. The sample size required in item 16 is very high due to the fact that we expect the control group to be very satisfied when answering this question(4). This sample size calculation was done in the statistical software G\*Power version 3.1.3 (18, 19).

**d) Summary of sample size calculations**

A total of 198 patients would enable us to find a medium-strong effect of the tested intervention in all variables except item 16 in the patient satisfaction questionnaire. The costs for increasing the number of patients 2.5 times to also find an effect in this variable is unreasonable, therefore this item will be a secondary research question. Thus we conclude that in theory 198 patients would be sufficient to answer all primary research questions. We expect that some patients will be lost to follow up. To cover for this we will aim to include 250 patients.

**2. Inclusion criteria**

All patients presenting to participating GP practices with otitis externa will be registered anonymously on a GP screening sheet. Patients accepting participation will be registered with more detailed data describing what inclusion criteria they fulfil. The inclusion criteria are:

- a) Has pain where VAS is  $\geq 2.5$  cm of maximum 10 cm (anchored as “moderate pain”).
- b) Will be staying in Australia at least 10 days (not leaving the country within a few days).
- c) Age  $\geq 16$  years.
- d) Not being pregnant.
- e) Seems to be cognitively intact.
- f) Speak English well enough to understand instructions and consent form.
- g) Has no large visual impairment that would preclude completion of the patient’s diary and questionnaire.
- h) Does not have Downs syndrome.
- i) Does not have obvious craniofacial abnormalities.
- j) Does not have diabetes mellitus.
- k) Does not have known immunodeficiency (HIV, Leukemia, etc).
- l) Is not taking immunosuppressant drugs or oral corticosteroids.
- m) Does not have known rupture of the tympanic membrane.
- n) Does not have grommet (tympanostomy tube).
- o) Does not have signs of systemic sepsis (body temperature  $>38.5^{\circ}\text{C}$ ), invasive fungal disease or perichondritis of the pinna.

### **3. Exclusion criteria**

Exclusion criteria and withdrawal are described in the section “Exclusion and withdrawal from treatment” on page 13.

### **4. Summary of Patient Characteristics**

Before applying the inclusion criteria we expect patients in the range of 1 - 80+ years of age with a mean age around 33 years and with approximately equal proportion of men and women (3). 92% of these unselected patients are not in need of a referral to an ENT specialist and 70% of them are not deemed to be in need of oral antibiotics (3). After applying the inclusion criteria we expect patients in the range of 16 – 80+ years of age and none of them needing a referral to an ENT specialist.

### **5. Patient log**

Patients complete a diary at the end of each day until symptom free or up to 10 days. This will be the patient log used.

## **D. Study medication**

### **1. Study product**

10 mg of prednisone or prednisolone packed in a gelatine capsule. The remaining space is filled with lactose. The volume of lactose is very small so most patients with lactose intolerance will not notice this.

### **2. Reference product**

Lactose packed in a gelatine capsule with identical appearance as capsules with active drug. The volume of lactose is very small so most patients with lactose intolerance will not notice this.

### **3. Randomisation procedure**

A sequence of 300 random numbers will be created. The outcome is transferred to a hardcopy with two columns. The left column indicates sequential order (1-300) and the right column contains the random number. The random numbers will be transformed to the letter A (for active substance) or P (for placebo) and thus creating a third column on the hardcopy. This hardcopy is labelled “randomisation code – version A”

300 empty medicine cans are sequentially numbered 1-300. They will be filled with active or placebo tablets according to the sequence of random numbers and then sealed.

### **4. Blinding procedure**

Another version of the hardcopy containing the randomisation sequence will be created containing one column of the sequence (1-300) and one column where the letters A and P are exchanged to other letters (X and Y) not revealing which group is active substance. This hardcopy is labelled “randomisation code – version B”

The first hard copy containing the true randomization code (“randomisation code – version A”) is put in a sealed envelope and locked into a safe. The second hard copy (“randomisation code – version B”) where the letters A and P are changed (making it impossible to know which group gets active substance) is given to the steering committee. The staffs involved in these procedures are not to disclose this information to anyone else until all statistical analysis is done. One exception is described in the section “Emergency decoding” on page 14.

Patients, General Practitioners meeting patients, Pharmacists dispensing drugs, the investigators and persons involved in statistical analysis will not be aware of group allocation until all statistical analysis are done (triple blind).

### **5. Packaging, labelling and storage**

The medicine cans will be labelled:

Study drug only to be dispensed to patients included in a research study (Otitis externa / Swimmer’s ear).

Can id: XXX (the sequential id number for this can)

For questions call: (Mobile phone number reachable 24/7 during the study period)

### **6. Product accountability**

The Clinical Trials Pharmacist Gemma Will at Calanna Pharmacy Woree maintains a record including medicine can number, batch number, expiry date, date and amount of study product received.

## **E. Therapy**

### **1. Treatment Schedule**

Treatment with the study product will commence immediately after accepting participation in the study. All enrolled patients are encouraged to take one capsule every 12 hours, in total eight capsules.

## **2. Compliance**

One extra question will be added in the final questionnaire where patients are asked how many of the expected eight capsules they took. We do not aim to collect medicine cans at the end of the study.

## **3. Concomitant therapy**

The study tablet will be additional therapy on top of any other therapy that the medical practitioner prescribes for this visit. The pharmacist will tick a list of drugs dispensed to the patient relevant for otitis externa (Appendix 8). We can then compare if prescribed medication differs between groups and adjust statistically for differences. The medical practitioner is informed that patients potentially to be included in the study must not already be on oral corticosteroids.

## **4. Concomitant diseases**

The inclusion criteria state that patients with diabetes mellitus or known immunodeficiency disorder are not to be included. The reason is that these patients have an increased risk for infections. Patients with Downs syndrome or patients having obvious craniofacial abnormalities are not to be included. The reason is that their anatomy in the external auditory canal deviates from normality and this might increase the risk for complications. Patients with cognitive or visual impairment are not to be included to avoid problems in informing patients or completing questionnaires.

## **F. Data collection**

### **1. Patient characteristics**

Age and gender will be noted on all patients by the GP on the "GP screening sheet". Findings during the physical examination will be described by GPs in the "inclusion sheet". Degree of pain will be estimated by patients on the "inclusion sheet" and thereafter in their daily diary.

### **2. Estimating compliance**

This will be asked for in the patient questionnaire.

### **3. Data for efficacy assessments**

Patients will complete a structured diary consisting of specific questions including a visual analogue scale for pain assessment. This diary is previously validated (4). When symptoms have resolved patients are asked to complete a final questionnaire, also previously validated (4). The final questionnaire will be complemented by questions concerning ethnicity and information regarding methods of ear cleaning if utilised by the medical practitioner. These questionnaires will provide sufficient data to answer all research questions posed.

## **G. Safety Management**

### **1. Clinical Safety Assessments**

In case a patients symptoms gets worse they are instructed to revisit their GP or, if their GP is unavailable, another medical practitioner. They are also instructed to inform the steering committee (via telephone or e-mail). The steering committee (see below) will regularly assess difference in

effect or adverse effect between groups. The committee will monitor differences in outcome or adverse events between groups and if necessary decide that the trial is stopped.

## **2. Adverse events**

An adverse event is defined as any unintended, unfavourable clinical sign or symptom that appears during treatment. The most likely adverse event should be increased pain. All adverse events are to be registered in the electronic log book belonging to this project together with an estimate if this is deemed to be related to the project or not. The responsibility for doing this lies with the steering committee.

In case an adverse event is noted the research support officer (Cindy Woods) informs the chair of the steering committee (see below) who decides if the steering committee should have an extra meeting.

## **3. Exclusion and withdrawal from treatment**

The following patient categories are to be excluded and withdrawn:

- Patients experiencing moderate worsening of pain after taking two or more doses of the study tablets and still have more study tablets to take.
- Patients experiencing severe worsening of pain while still on the study tablet.
- Patients experiencing fever  $>38.5^{\circ}\text{C}$  while still on the study tablet.
- Other types of adverse events need to be evaluated case by case.

Patients experiencing any type of adverse effect mentioned above are instructed in the written information to immediately contact their GP (or nearest Emergency department if their GP is unavailable). The patient information will also tell those patients that they must immediately stop taking the “study tablets”. Furthermore they are instructed to notify the steering committee. Patients are also withdrawn from the study if it is the wish of the patient.

## **4. Discontinuation of the study**

The study is to be discontinued in any of the following cases:

- If the use of oral corticosteroids results in a more favourable outcome the reality is that oral corticosteroids are currently not officially recommended and only advocated by a very small minority of GPs (3). Thus, to actually influence future treatment guidelines the positive stopping rule is that the study should only be stopped in case the advantage of adding oral corticosteroids has a very low p-value for at least two of the primary research questions:  
25% recruited ( $p < 0.0000001$ )  
50% recruited ( $p < 0.000001$ )  
75% recruited ( $p < 0.00001$ ).
- In case patients given oral corticosteroids show a slower recovery than patients given placebo (number of days to resolution of pain), the negative stopping rule is  $p < 0.001$ .
- In case patients given oral corticosteroids show more serious adverse events than patients given placebo, the stopping rule is  $p < 0.05$ .

- In case patients getting placebo treatment show more serious adverse events (other than a slower recovery) than patients receiving oral corticosteroids, the stopping rule is  $p < 0.001$ .

A decision to discontinue the study can only be made by the steering committee with at least 50% of members participating. The chair of the steering committee (see below) can decide to temporarily pause the study in case it is difficult to arrange a meeting with the full steering committee.

### **5. Emergency decoding**

In case the steering committee finds a statistical difference between groups in an interim analysis (as described above in section "Discontinuation of the study") and if they need to clarify group assignment to make a decision, then they will be given access to the "randomisation code – version A". In case a patient should be acutely severely ill a decoding for that patient may also occur.

## **H. Statistical analysis**

### **1. Time to resolution of pain**

The VAS in patient diary measuring pain will be used to determine the number of days until pain is almost ( $\leq 10$ mm of max 100mm) or completely (0mm of max 100mm) gone. Groups will be compared using log rank test. Cox regression will be used in case baseline differences exist between groups. If ethnicity is of importance it will be a confounding variable in the Cox regression. Furthermore, in that situation sub analysis will be made separately for Indigenous people (although the study is not powered for this sub analysis).

### **2. Lost hours**

Items 16-19 in the patient diary are summed up to a total amount of "lost hours" per patient in respect of need for bed rest, activity limitation, paid work missed and need for paid child/elder care. Effect size with 95% confidence interval is calculated. Total number of hours in each area will also be compared between groups using Mann-Whitney's test (skewed data). Should baseline differences exist between groups we will investigate using covariance analysis.

### **3. Satisfaction with symptom resolution**

Item 10-16 in the patient satisfaction questionnaire are used. We primarily intend to calculate effect size with 95% confidence interval. Secondly, we will compare groups with Mann-Whitney's test. However, should any baseline differences exist then we will analyse with Logistic regression. In such case the outcome of the item will be dichotomised with the median value as cut off limit and used as dependent variable. Treatment and variables that differ between groups at baseline will be independent variables.

### **4. Secondary research questions**

If oral steroids reduce the need for unplanned revisits or the need for exclusion due to worsening of symptoms will be analysed using Fishers exact test. The importance of ethnicity will be evaluated in the research question time to resolution of symptoms where ethnicity will be a covariate. The question if corticosteroids increase patient satisfaction concerning time to resolution of normal activities will be analysed as the other questions about patient satisfaction with symptom resolution (see above).

## **VI. Ethical requirements**

### **A. Declaration of Helsinki**

The study will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964 and later revisions.

### **B. Ethical approval**

It is the responsibility of the chief investigator to obtain approval of the Study Protocol from appropriate ethics committee and to keep the ethics committee informed of any Serious Adverse Events and amendments of the protocol.

### **C. Informed consent**

All patients will be asked for to sign a written consent form.

### **D. Research involving Aboriginal and Torres Strait Islander people**

This project does not primarily target Aboriginal or Torres Strait Islander people. The study is not powered to investigate differences between ethnic groups. However, in case any difference between ethnic groups are found these findings and possible interpretations will be discussed with representatives from community controlled health organisations before being presented publicly.

### **E. Patient data protection**

Patients not consenting to participate will be noted anonymously with age and gender. A password protected code key, with the possibility to re-identify participants accepting participation, will be kept separate from the actual data file. Only the principal investigator and the co-investigators of this project will have access to data.

## **VII. Management and Monitoring**

### **A. Trial Management Group**

The trial management group consists of two Professors in general practice (Ronny Gunnarsson and Clare Heal), one Professor in ear-nose-throat diseases (Anders Cervin), one Professor in infectious diseases (John McBride), a GP with extensive interest and clinical experience of otitis externa (Graeme Balch) and a social scientist (Cindy Woods). All participating Professors have previous experience of randomised controlled clinical trials. The different expertise all members bring to the team cover all relevant aspects of the illness otitis externa. This constellation is ideal to study acute otitis externa among patients in general practice.

The trial management group plans the study (with final approval from the steering committee), makes ethics application, applies for funding and deals with all practical problems that may occur.



## **B. Independent data-monitoring committee (IDMC)**

This study is an investigator initiated trial without funding or other support from a drug company. Furthermore, it can be considered as a rather small clinical trial with only 250 participants evaluating a treatment that is already used in clinical praxis (despite scientific evidence). For these reasons a slightly simpler management and monitoring arrangement was considered sufficient.

This trial does not have an IDMC. The trial steering committee (see below) will fulfil this function. The independence of the steering committee is ensured by only having one member directly involved in the study while the other two are not involved more than being a member of the steering committee.

## **C. Trial Steering Committee**

The steering committee has the overall responsibility for the scientific quality of the study and the responsibility to decide if the study needs to be discontinued early. The trial steering committee consists of Associate Professor Ronny Gunnarsson (James Cook University), Associate Professor Peter Morris (Menzies School of Health Research) and Associate Professor Malcolm MacDonald (James Cook University). Ronny Gunnarsson will be chairman of the steering committee and as such he summons the committee for an initial meeting to approve the study protocol. The committee also meets when 25%, 50% and 75% of data collection is completed.

The steering committee nominates a vice chair within the committee. The committee should strive for unity in decisions. If unity cannot be reached then decisions is made by voting. The chairs vote counts as two votes only in case of voting with an indecisive outcome.

## **VIII. Miscellaneous**

### **A. Liability / Insurance**

James Cook University has insurance for clinical trials run by the University.

### **B. Reporting and communication of results**

The outcome will be presented in a peer reviewed scientific publication in an international journal. Furthermore, results will be presented at a scientific congress.

### **C. Clinical trials databases**

Once ethics approval is obtained the study will be registered in the following databases:

- Australian New Zealand Clinical Trials Registry (ANZCTR)
- ClinicalTrials.gov
- Researchweb.org/is/jcu

## IX. Budget

	Direct expense	In kind contribution
Participating GPs		12,500
Participating pharmacists		12,500
Salary Dr Graeme Balch		25,000
Salary A Prof Ronny Gunnarsson		15,000
Salary A Prof Malcom MacDonald		2,500
Salary A Prof Peter Morris		2,500
Salary Dr Cindy Woods		6,000
Salary Prof John McBride		2,000
Salary A Prof Clare Heal		2,000
Salary Prof Anders Cervin		2,000
Costs for website		500
Petrol costs for initial contact, distribution of instructions and tablets	\$ 1,000	
Costs for active drug and placebo tablets in unmarked tablet containers. Costs for randomisation procedure.	\$ 1,700	
Printing of Study protocols informed consent, written information	\$ 100	
Stamps and envelopes for prepaid response envelopes	\$ 350	
<b>Sum of costs</b>	<b>\$ 3,150</b>	<b>\$82,500</b>

## X. Study time frame

The study will commence as soon as ethics approval is given. The first phase is practical preparations. Data collection will occur during the wet season from November 2014 until 250 patients are included:

	2014			2015		
	April - May	June - Oct.	Nov.- Dec.	Jan.- April	May- June	July- Dec.
Planning & ethics approval						
Practical preparations						
Data collection						
Analysis & writing						
Submission (and author responses to reviewers comments)						

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