OSTRICH:

A randomised double blind placebo controlled clinical trial using **O**ral **ST**eroids for the **R**esolution of otitis media with effusion (OME) **I**n **CH**ildren.

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This protocol has been authorised by:

Name	Role	Signature	Date
Prof Kerry Hood	Director of Clinical Trials		13/3/15
Prof Christopher C Butler	Chief Investigator		11/03/2015.
Dr Nicholas A Francis	Chief Investigator		11/03/15

General Information This protocol describes the OSTRICH clinical trial, and provides information about the procedures for entering participants into the trial. The protocol should not be used as a guide, or as a reminder for the treatment of other patients. Every care has been taken in drafting this protocol; however, corrections or amendments may be necessary. These will be circulated to the known Investigators in the trial, but centres entering patients for the first time are advised to contact the trial coordinating centre, South East Wales Trials Unit (SEWTU) in Cardiff to confirm that they have the most up-to-date version of the Protocol in their possession. Problems relating to the trial should be referred, in the first instance, to SEWTU.

Compliance This trial will adhere to the conditions and principles which apply to all clinical trials as outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended, EU Directive 2001/20/EC, EU Directive 2005/28/EC and the Principles of Good Clinical Practice (GCP). It will be conducted in compliance with the Protocol, the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI2004/1031), as amended, the Research Governance Framework for Health and Social Care (RGFR) (Welsh Assembly Government November 2001 and Department of Health 2nd July 2005), the Data Protection Act 1998, and other regulatory requirements as appropriate.

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Please contact the Trial Manager (TM) for general queries and supply of Trial documentation

Randomisations:

Randomisation

Randomisation of trial participants will be achieved through the use of unique pre-labelled trial medication packs. **Please contact the Trial Manager at South East Wales Trials Unit on 07891830421 if unblinding is required.**

Clinical queries:

Clinical queries

All clinical queries should be directed to the Trial Manager (tel: 029 2068 7609) who will direct the query to the most appropriate clinical person.

Serious Adverse Events (SAE):

SAE reporting

Where the adverse event meets one of the serious categories, an SAE form should be completed by the responsible clinician and faxed to the OSTRICH Trial Manager within 24 hours upon becoming aware of the event (fax: 029 2068 7612). (See Section 12 for more details).

Table of Contents

Glossary of abbreviations

AE	Adverse Event
AR	Adverse Reaction
BNF	British National Formulary
CI	Chief Investigator
CRF	Case Report Form
CPRD	Clinical Practice Research Datalink
CTA	Clinical Trials Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
DSUR	Development Safety Update Report
ENT	Ear, Nose and Throat
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
GP	General Practitioner
GMP	Good Manufacturing Practice
HB	Health Board
HTA	Health Technology Assessment
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISRCTN	International Standard Randomised Controlled Trial Number
MHRA	Medicine and Healthcare products Regulatory Agency
NHS	National Health Service
NICE	National Institute for Clinical Excellence
NIHR	National Institute for Health Research
NISCHR CRC	National Institute for Social Care & Health Research Clinical Research Centre
OME	Otitis Media with Effusion
PEDS-QL	Paediatric Quality of Life Inventory
PEDW	Patient Episode Database for Wales
PI	Principal Investigator
PIS	Patient Information Sheet
QALY	Quality-adjusted Life Years
QL (QoL)	Quality of Life
QP	Qualified Person
R&D	Research and Development

REC	Research Ethics Committee
RGFR	Research Governance Framework for Health and Social Care
SAE	Serious Adverse Event
SAIL	Secure Anonymised Information Linkage
SAR	Serious Adverse Reaction
SEWTU	South East Wales Trials Unit
SOP	Standard Operating Procedure
SmPC	Summary Product Characteristics
SSI	Site Specific Information
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

1 Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
1	V2.0	19.06.2013	Cherry-Ann Waldron	• Amendment made to where follow up visits will be conducted: e.g. followed up in ENT or Audiology outpatient clinics (p.21) and Figure 1 amended (p.16), • Additions made to inclusion criteria: First time in the OSTRICH trial, ability of parent/carer to understand and give informed consent, does not already have grommets (ventilation tubes) (p.21), • Additions made to exclusion criteria: Ear infection, Kartagener's or Primary Ciliary Dyskinesia, existing known sensory hearing loss, undergoing cancer treatment, on a waiting list for grommet surgery and anticipates having surgery within 5 weeks and unwilling to delay it (p.22), • Pharmacovigilance section amended to include section on expectedness, clarification on who is responsible for assessing causality and clarification of timeline for SUSARs e.g. 'day zero is defined as the date the SAE form is initially received at SEWTU' (p.31). • Additional procedure added to 5 week follow-up: At the 5 week follow up appointment any unused trial medication will be collected and returned to pharmacy for disposal (p.35), • A number of non-substantial amendments have also been made, such as correction of errors and rewording for clarification (e.g. definition of hearing resolution 'less than or equal to 25/20 dBHL', removing age restrictions on method of audiometry used, additional audiometry methods included and updating the trial management group members). Also, formatting such as increasing font size of telephone/fax numbers etc.
2	V3.0	08.10.2013	Cherry-Ann Waldron	• Rewording made to inclusion/ exclusion criteria: the inclusion criterion *'does not already have grommets (ventilation tubes)*' changed to the exclusion criterion of '*child already has grommets (ventilation tubes)*' (p.23), • Changes to study procedure: a designated member of the OSTRICH team (where possible) or the participant's parent will collect the Trial pack from Pharmacy (p.25, p.29),

				• Unblinding telephone number added (p.5, p.26), • Amendment made to the different options that a parent can choose when withdrawing their child from the study (p.27), • Adverse events CRF completed at 5 week follow up as well as in parent diary to ensure all non-serious adverse reactions and events are recorded (p.32), • Changes to study procedure: Data linkage used to identify healthcare consultations during the 12 month follow up period in secondary care and primary care (where possible) (p.38, p.43), • Timeframe windows for follow up added e.g. + 1 week for 5 week follow up, +/- 2 weeks for 6 and 12 month follow ups (p.42), • Changes to protocol: Pharmacovigilance section amended to include section on expectedness, clarification on who is responsible for assessing causality and clarification of timeline for SUSARs e.g. 'day zero is defined as the date the SAE form is initially received at SEWTU'. • Patient Information Leaflet terminology changed to Medication guidance leaflet.
3	V3.1	20.01.2014	Cherry-Ann Waldron	• Unblinding telephone number amended (p.5, 26). • Fax number and Trial team- Trial Administrator details updated (p.5). • Clarification that study information will be sent with clinic referral letter where possible (p.23) • Clarification that Medication guidance and instructions for use leaflet given with trial pack (p.26). • Remove 'taste' from the characteristics of the placebo matched to the active (p.27). • Reverting to previous version of protocol – No Adverse Event CRF to be completed at 5 weeks (p.32). • OSTRICH nurse, defined to include Clinic nurse, research nurse or Clinical studies research officer. Clarification that qualified person provides guidance on medication (e.g. Clinician or Nurse) (p.36). • Procedures of OSTRICH nurse updated to include giving out/administering questionnaire booklet and Medication guidance and instructions for use leaflet (p.36).
3.1	V4.0	24.03.2014	Nick Francis	• Addition of sub-study on qualitative sub-study will explore parents' understanding of the treatment options available to them and the views about the role of shared decision making in the context of managing glue ear, as well as their views on the use of oral steroids for glue

				ear. • Addition to 'supply, packaging, storage and reconciliation of trial medication' section, to say there is overage and extra tablets are to be returned at the 5 week follow up appointment.
4.0	V4.1	06.06.2014	Cherry-Ann Waldron	• Tightening up wording in the inclusion criteria for the timeframe of audiometry confirmed hearing loss (p.23). • Formatting of 'withdrawal and loss to follow up section' (p.27). • Addition of sending reminders for follow up appointments (p.28), and contacting parents regarding missed appointments, with option of answering short questionnaire over the telephone (p.36). • Timeframe windows for follow up e.g. + 1 week for 5 week follow up, +/- 2 weeks for 6 and 12 month follow ups moved from 'Analysis' section (p.43) to 'Data collection/assessment' section (p.37).
4.1	V5.0	11.03.2015	Cherry-Ann Waldron	• Definition of a temperature excursion to be reported to SEWTU e.g. 27 ºC (25ºC with an additional tolerance of 2ºC) (p.29).

2 Synopsis

Short title	Oral steroids for resolution of otitis media with effusion (OME) in children
Acronym	OSTRICH
Internal ref. no.	SPON1030-11
Clinical phase	III (MHRA risk category B)
Trial design	Individually randomised double blind controlled clinical trial
Trial participants	Children aged 2-8 years who have had symptoms including hearing loss attributable to OME for at least three months and have been assessed in an Ear, Nose, and Throat (ENT) outpatient clinic and diagnosed with bilateral OME and significant hearing loss confirmed by audiology.
Planned sample size	380 participants will be recruited (190 subjects in each of the active arm and the placebo arm)
Follow-up duration	Participants will be followed up at 5 weeks and then after 6 and 12 months from the date of randomisation. The primary outcome will be measured at 5 weeks from the start of treatment.
Planned trial period	36 months
Primary objective	To determine the clinical and cost effectiveness of a 7 day course of oral prednisolone (steroid) on improving hearing in the short term in children with bilateral OME with hearing loss for at least 3 months.
Secondary objectives	To assess the effect of the intervention on hearing, cost–effectiveness, resolution of OME, adverse effects, symptoms, functional health status and health related quality of life in the longer-term (up to 12 months).
Primary endpoint	The proportion of children with acceptable hearing, as defined for this Trial, at 5 weeks from the start of treatment.
Secondary endpoints	• The effect of the intervention on achieving satisfactory hearing at 6 and 12 months, • The effect of the intervention on resolution of OME as assessed by tympanometry and audiology, • The short and longer-term cost-effectiveness, • Rates of ventilation tube insertion (grommets) at 6, and 12 months, • Adverse effects, • Effect on self or parent reported symptoms, • Effect on functional health status, • Health Related Quality of Life (QoL).
Investigational medicinal products	Prednisolone Sodium Phosphate (steroid) Matching placebo
Form	Soluble Tablet (5mg)

Dose	20mg for 2-5 year olds; 30mg for 6-8 year olds; given once daily for 7 days
Route	Oral

3 Trial summary

3.1 Trial Summary

Otitis media with effusion (OME), also known as glue ear, is an accumulation of fluid in the middle ear. About 80% of children have had OME by the age of 4 years. While OME usually gets better by itself, for thousands of children every year it can result in deafness, which can affect speech and social development and result in depression, behavioural and attention disorders. If deafness lasts longer than 3 months, children are usually offered hearing aids or a grommet operation (insertion of ventilation tubes through the eardrum (tympanic membrane). Both hearing aids and grommet insertion have risks and side effects, are costly, and require repeated visits to hospital clinics. In the UK, 23,000 children had grommets inserted under general anaesthetic in 2009. Finding a simple, safe, acceptable, effective treatment for use in general practice that can also be used in children in the first four years of life would be of great benefit to children, their families and the National Health Service (NHS).

Many oral medications have been shown not to work for OME. However, there is evidence from pooling findings from small trials that a short course of oral steroids may work. But these trials were either too small, of too short duration, or of too poor quality to give a definite answer. So there is currently uncertainty about meaningful, longer-term benefit.

The aim of the OSTRICH trial is to determine if a short course of oral steroids improves the hearing of children with OME in the short and longer term. A short course of oral steroids is a frequently used treatment for acute asthma in young children, and is considered safe.

We aim to recruit 380 participants (children aged 2-8 years) from Ear, Nose and Throat (ENT) departments from approximately seven Hospital sites in Wales. A designated OSTRICH trial trained Clinician will seek informed consent from parents of children aged 2-8 years of age who are seen in a participating hospital ENT department with symptoms attributable to OME for at least 3 months and with confirmed bilateral hearing loss. Participants will be randomised to take a course of oral steroid, or a matched placebo, for one week. Measurements, including hearing and assessment of quality of life, (QoL) will be made just before the start of treatment and at 5 weeks, 6 and 12 months after the day of randomisation.

The main outcome will be satisfactory hearing (as assessed and confirmed by audiology) in at least one ear in children under approximately 3 years, and in both ears together in children 3 years of age and over) five weeks after randomisation (4 weeks after

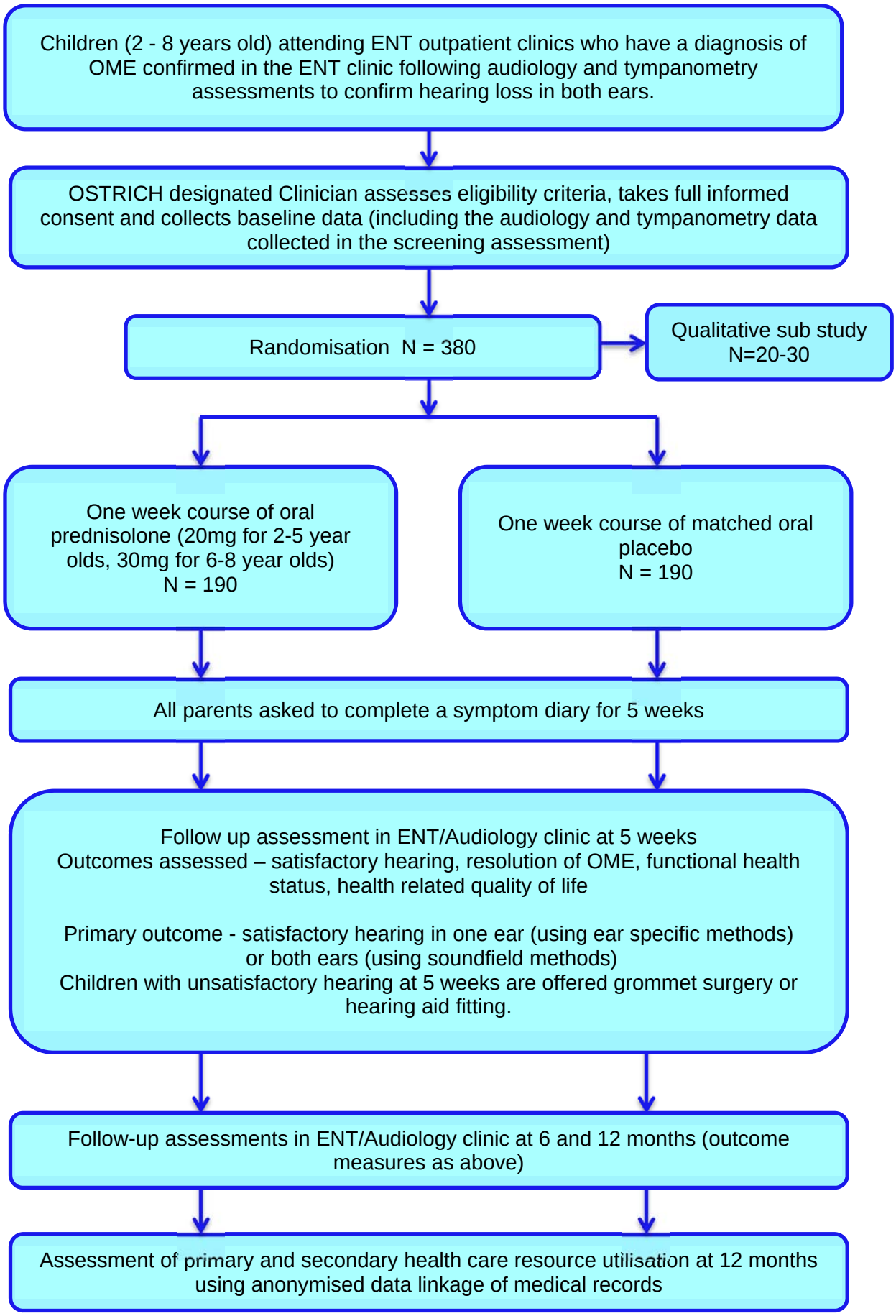
completion of the treatment course). Other outcomes will include satisfactory hearing in the long term, clearing of OME, children's symptoms as recorded in a diary, adverse effects, functional health status and QoL, resource use and cost, and cost effectiveness.

A qualitative sub-study will explore parents' understanding of the treatment options available to them and the views about the role of shared decision making in the context of managing glue ear, as well as their views on the use of oral steroids for glue ear. This is described in detail in section 17.

3.2 Trial schema and Participant flow

The schedule of events and participant flow for the trial is summarised in Figure 1. Full details of assessments performed (clinical and non-clinical) are presented in Section 14. Figure 1 demonstrates the trial schema and participant flow.

Figure 1: Trial Schema and participant flow diagram



4 Introduction

4.1 Background

Importance of the problem

OME is the commonest cause of hearing loss in children in the UK, and up to 80% of children are affected by OME by 4 years of age[1]. Overall, the prognosis for OME is good, with over 50% of OME episodes resolving spontaneously within 3 months and 95% within 1 year. However, 30-40% of children have recurrent OME episodes, and 5% of preschool children aged 5 years have persistent (longer than 3 months) bilateral hearing loss associated with OME[2].

Hearing loss from OME can have an important impact on children's mood, communication, concentration, learning, socialisation and language development. This may affect other family members and family function. OME in early childhood can affect IQ, behaviour, and reading into teenage years[3].

UK National Institute of Clinical Excellence (NICE) guidelines (2008) for OME management recommend a 'watchful waiting' period of 3 months, with referral to a ENT department if hearing is significantly affected, OME persists for longer than 3 months, or if there is suspected language or developmental delay[4]. Treatment options for these children are limited to hearing aids or surgical insertion of ventilation tubes (grommets) through the tympanic membrane. Hearing aids are an effective treatment, but this intervention is not problem-free: children often find them uncomfortable, may feel self-conscious, and become a target for bullying[5].

Although the diagnosis of OME in primary care has increased over the last decade, the number of grommet operations performed in England fell from 43,300 in 1994-1995 to 25,442 in 2009-2010, primarily as a result of the 'watchful waiting' strategy[6]. However, OME remains the commonest reason for childhood surgery in the UK and comprises a considerable workload for hospital ENT departments. Furthermore, there is wide variation in the rate of grommet surgery between regions that is unlikely to be explained by variation in disease. In Wales, there is six-fold variation in the European age-standardised rates of grommet surgery between the highest and the lowest local authorities[7].

Both hearing aids and surgery require referral to secondary care with major cost consequences: The recent Department of Health commissioned 'McKinsey' report states that the NHS could save £21 million per year by reducing grommet insertion by a further 90%, a procedure that they assessed as being 'relatively ineffective'[8]. This position has

been challenged. Deafness Research UK and the 2009 ENT UK Position Paper conclude that reducing access to grommets will disadvantage thousands of children who have a genuine need of treatment[9,10].

4.2 Rationale for current trial

Antibiotics, topical intranasal steroids, decongestants, antihistamines and mucolytics are all ineffective treatments for OME[11-13]. However, Cochrane systematic reviews have found sufficient evidence for the effectiveness of both oral steroids and autoinflation (AI) devices in resolving OME in children to recommend further research [12].

Currently, the HTA funds a trial of an AI device in children with OME aged 4-11 years[14]. However, 80% of children are affected by OME before the age of 4 years at the time when language development is most rapid and hearing loss has its greatest effect on language development[3]. Therefore, alternatives to hearing aids or surgery for children aged less than 4 years (who are unable to use the AI device being evaluated in the Williamson study) are required.

There is evidence from *in vitro* and animal models that steroids reduce effusions and middle ear pressure[15-18]. Various mechanisms have been proposed for a role for steroids in resolving middle ear effusions, including: (i) reducing arachidonic acid and associated inflammatory mediators; (b) shrinking peri-eustachian tube lymphoid tissue; (c) enhancing secretion of eustachian tube surfactant with a resultant improvement in tubal function; and (d) reducing middle ear fluid viscosity by its action on mucoproteins[19].

The AI device trial by Williamson et al (2009) evaluated topical intranasal steroids for children with OME in general practice and found they are unlikely to be clinically effective for OME[14]. Topical steroids applied through the nose would not be expected to reach the middle ear. However, systemic steroids do reach the middle ear epithelium and modulate OME in animal models[20].

The latest update of our Cochrane review on oral or topical steroids for OME (last search August 2010) found no benefit from intranasal steroids[12]. However, the review did identify evidence of a statistically significant benefit from oral steroids plus antibiotics versus antibiotics alone for OME (5 studies, 409 participants, 23% in the intervention group and 47% in the control group with persistent OME at follow up), and a trend towards a significant benefit for oral steroids versus placebo (3 studies, 108 participants) in the short term. Oral antibiotics alone are not effective. The only study to assess the effect of oral steroids on hearing as an outcome was underpowered.

Studies included in the systematic review were short-term, underpowered, often poorly described inclusion criteria and/or did not assess hearing at the time of inclusion, used

ears rather than children as the unit of analysis, and used intermediate outcome measures, such as tympanometry results, rather than improved hearing. We found no cost effectiveness studies of oral steroids for OME.

There is therefore insufficient evidence to recommend oral steroids as a treatment for persistent OME because of inadequate evidence about short-term effect on hearing and cost-effectiveness, and absence of evidence about longer-term effects.

4.3 Potential harms from oral steroids

Studies included in our Cochrane review reported no significant adverse effects. However, the number of participants was too small to rule out that possibility. Short courses of prednisolone are widely used in treating children with acute asthma and adverse events (AEs) are extremely rare: when they do occur, they are largely limited to behavioural disturbances and dyspepsia and resolve on withdrawal of the steroid drug. The safety of multiple short courses of oral steroid therapy has been evaluated[21]. Short courses of oral steroids such as prednisolone do not have lasting negative effects on bone metabolism, bone density, adrenal gland function or weight or height, even if used on several occasions over the course of a year[22].

4.4 Summary

There is an important evidence gap regarding clinical and cost effectiveness of short courses of oral steroid treatment for OME. Identifying an effective, safe, cost effective, acceptable non-surgical intervention for OME in children (including those in the first four years of life) for use in primary care remains an important research priority.

5 Trial objectives

5.1 Primary objective

To determine the clinical and cost effectiveness of a 7 day course of oral prednisolone (steroid) on improving hearing over the short term in children with bilateral OME, as diagnosed at an ENT outpatient clinic, who have had symptoms attributable to OME present for at least 3 months, and current significant hearing loss (demonstrated by audiometry).

5.2 Secondary objectives

To assess the longer –term (up to 12 months) effect of the intervention on:

- hearing,

- resolution of OME,
- grommet surgery rates,
- symptoms,
- adverse effects,
- functional health status,
- quality of life (QoL),
- cost-effectiveness.

6 Trial design

This is a double-blind, individually randomised, placebo-controlled trial involving children with persistent OME and significant hearing loss. We aim to recruit 380 children (2-8 years of age) who will be randomised to receive a 1 week course of oral prednisolone or a matching placebo. All participants will be followed-up for 12 months.

7 Centre and Investigator selection

This trial will be conducted in ENT clinics at NHS hospital sites in Wales. If necessary, we will extend the study to include NHS hospital sites in England. All hospital sites must have an ENT clinic where outpatients with suspected OME are assessed, and appropriate audiometry services.

Before recruitment commences at a site, a Principal Investigator (PI) will be identified for that site. A qualified ENT consultant will take on the role of the PI and will be the designated OSTRICH trial clinician. The PI may delegate trial related activities to appropriate trained and qualified personnel according to staff responsibilities and job descriptions. This will be documented in a trial specific Delegation of Responsibilities form.

Before any site can begin recruitment it is the responsibility of the PI to ensure the following documents are received by the OSTRICH Trial Manager (TM) (see contact details on page 5):

- Site Specific Information (SSI) approval,
- A signed Trial Agreement (PI, sponsor and site signatures),
- Completed Signature List and Roles and Responsibilities document,
- Completed contacts list of all site personnel working on the trial,
- Consent form and PIS on Trial site letter headed paper,

- Site initiation training.

Upon receipt of all the above documents and confirmation from the Medicine and Healthcare Products Regulatory Agency (MHRA) that the site and PI has been added to the OSTRICH Clinical Trial Authorisation (CTA), the OSTRICH TM will send a confirmation letter to the PI, detailing that the site is now ready to recruit participants into the trial. This letter must be filed in each centre's Site File. Along with this confirmation letter, the centre should receive their trial drug supplies and a Trial Pack holding all the documents required to recruit a patient into the OSTRICH Trial.

8 Participant selection

Children are eligible to join the trial if they meet the following inclusion criteria (section 8.1) and do not meet any of the exclusion criteria (section 8.2). All queries about patient eligibility should be directed to the OSTRICH Trial Manager (TM) before randomisation.

Children will be identified in ENT outpatient clinics and followed up in ENT or Audiology outpatient clinics.

8.1 Inclusion criteria

- Aged 2-8 years (reached 2nd birthday and not yet reached 9th birthday),
- Had symptoms of hearing loss attributable to OME for at least 3 months (or had audiometry proven hearing loss for at least 3 months),
- Diagnosis of bilateral OME made in an ENT clinic on the day of recruitment or during the preceding week,
- Audiometry confirming hearing loss of more than 20 dBHL averaged within the frequencies of 0.5, 1, 2, and 4 KHz in both ears by pure tone audiometry ear specific insert visual reinforcement audiometry (VRA) or ear specific play audiometry, or hearing loss of more than 25 dBHL averaged within the frequencies of 0.5, 1, 2, and 4 KHz by soundfield VRA or soundfield performance/play audiometry in the better hearing ear, on the day of recruitment or within the preceding 14 days.
- First time in the OSTRICH trial,
- Ability of parent/carer to understand and give informed consent,

8.2 Exclusion criteria

- Children who are currently involved in another CTIMP or have participated in a CTIMP during the last 4 months.
- Children with current systemic infection or ear infection,

- Children with cleft palate,
- Children with Down's syndrome,
- Children with diabetes mellitus,
- Children with Kartagener's or Primary Ciliary Dyskinesia,
- Children with renal failure, hypertension or congestive heart failure,
- Children with confirmed, major developmental difficulties (e.g. are tube fed, have chromosomal abnormalities),
- Children who have taken oral steroids in the preceding four weeks,
- Children with a condition that increases their risk of adverse effects from oral steroids (i.e. on treatment likely to modify the immune system or who are immunocompromised, such as undergoing cancer treatment),
- Children who have been in close contact with someone known or suspected to have Varicella (chicken pox) or active Zoster (Shingles) during the three weeks prior to recruitment and have no prior history of Varicella infection or immunisation.
- Children with existing known sensory hearing loss,
- Children who already have grommets (ventilation tubes),
- Children who are on a waiting list for grommet surgery and anticipate having surgery within 5 weeks and are unwilling to delay it.

9 Recruitment and randomisation

9.1 Number of participants

We aim to recruit a total of 380 participants over a 12-month period although this could take longer. We anticipate that each site will be able to recruit an average of 4-5 participants per month. We will review the total time allotted to recruitment as the trial progresses.

9.2 Recruitment process

This protocol will use the term 'parent' to refer to the person with legal responsibility for the child, therefore, as applied in this protocol the term also encompasses carers (parents and carers designated as legal guardians).

9.2.1 Informing parents of potentially eligible children about the trial

Where possible, parents of children who have been referred to a participating ENT clinic for probable OME will be sent a letter informing them about the trial, and a participant information sheet (PIS), along with their invitation to attend the clinic.

9.2.2 Identification of potentially eligible children

Parents of children attending ENT clinics with bilateral hearing loss or a diagnosis of OME will be approached about the trial by an ENT clinician (doctor, nurse or audiologist). Each child will have an audiometry assessment and a clinical assessment (both routine procedures for those attending these clinics) before they can be assessed for eligibility to enter the trial.

When attending the clinic, parents of potentially eligible children will then be invited to speak with a designated clinical member of the OSTRICH trial team. This individual will explain the trial to the child's parent and provide them with a written participant information sheet (PIS). If the parent has already received the PIS with their clinic invitation, then the designated individual will go through this with the parent. They will ensure that the parent has had enough time to consider participation and answer any questions that the parent may have, and take informed consent if they are willing for their child to participate. Age appropriate pictorial information sheets will also be provided for children who are old enough to use them.

9.3 Informed Consent

Informed consent will be taken by suitably qualified, experienced and trained personnel in accordance with the GCP directive on taking consent and before any trial related procedures are undertaken. Written informed consent will be obtained from the child's parent or legal guardian. Parents will be notified that they can withdraw their consent for their child's participation in the trial at any time during the trial period.

For all children, the person taking consent will assess the child's capacity to understand the nature of the trial. Age appropriate information sheets will be supplied where appropriate and the views of children capable of expressing an opinion will be taken into account. Children who are deemed to have capacity will be asked to sign an age appropriate assent form.

We will comply with Welsh language requirements and the PIS, Consent Form and any other required participant documentation will be available in Welsh. However, all documentation used for data collection (i.e. outcome measures) will remain in English as they are designed and validated in English.

9.4 Randomisation

Randomisation will be coordinated centrally by South East Wales Trials Unit (SEWTU). The randomisation schedule will be stratified and will be prepared and held by the Trial

Statistician (TS). SEWTU will provide the Investigational Medicinal Product (IMP) manufacturer (Piramal Healthcare UK Limited) with a list of random allocation numbers linked to either steroid or placebo, which will be used to label the trial medication packs. Each medication pack will be labelled with a unique identification number (trial medication pack number). The trial medication packs (Trial Pack) will be delivered to trial sites by the IMP Manufacturer, Piramal Healthcare UK Limited.

As children are recruited, they are assigned the next vacant Participant Identification number (PID). Participants will be randomised to receive either the steroid or the matching placebo and upon randomisation the next sequentially numbered Trial Pack will be allocated to the participant by the Site Pharmacy. A designated member of the OSTRICH trial team (where possible) or the participant's parent will collect the pack from Pharmacy on behalf of the participant.

Trial Pack(s) will only be released once informed consent has been obtained and a Consent Form signed. Participant randomisation will be considered to have occurred once a Consent Form has been signed and the Trial Pack opened. The Trial Pack number will then be entered onto the participant's CRF.

9.4.1 Blinding

Participants, parents, clinic staff and local site members of the OSTRICH trial team should all remain blind to treatment allocation. The unique identification number on each Trial Pack will be linked to the randomisation file. If clinicians at sites are providing clinical treatment for a serious adverse event (SAE) they can contact the South East Wales Trials Unit (SEWTU) for unblinding (see section 12.1).

9.4.2 Un-blinding

The medication used in this trial is a licensed product (or its matching placebo) however it is being used outside its licensed indication. Parents will be provided with information about the medication their child may be on (i.e. steroid or its placebo) and the most likely adverse events (AEs) that may necessitate unblinding. Furthermore, if such a SAE (section 12.1) occurs or unblinding is required for any reason, we will provide a 24 hour unblinding service.

OSTRICH local site researchers/clinicians will advise the parent to contact NHS Direct, their primary care out-of-hours provider, or the emergency ambulance service if their child should require emergency out-of-hours medical attention. The parent will be advised to ensure they provide the participant's Trial Pack, Medication guidance leaflet

and other trial documentations to the treating clinician(s). This information will notify the treating clinician(s) that the participant is either taking Prednisolone soluble tablets, or its placebo orally.

A Medication guidance and instruction for use leaflet will be given with the trial medication, which will include information on unblinding. In the event that a clinician treating a trial participant needs to know the trial medication that a participant is taking (or has taken), they can request unblinding of that participant's trial medication by telephoning the number below 24 hours a day. Randomisation lists will be kept in a secure location that is accessible to staff providing the unblinding service.

Contact SEWTU for unblinding:

Tel: 07891 830421

9.5 Screening logs

A screening log of all children approached, those eligible and ineligible and those recruited and not recruited and a brief reason for non-recruitment using non-identifiable data will be kept at each trial site. This information will be recorded so that any bias from differential recruitment can be detected. The screening log will be faxed or a photocopy provided to the OSTRICH TM at regular intervals, to be agreed with the Trial site staff, to allow monitoring of recruitment progression.

10 Withdrawal & loss to follow-up

10.1 Withdrawal

Parents may withdraw consent for their child to participate in any aspect of the trial, at any time. Declining to participate or withdrawing from the trial will not affect the care of patients.

Parents who wish to withdraw their child from the trial will be asked to decide whether they wish to withdraw their child from:

- further treatment but participate in all further data collection,
- active follow-up but allow existing data and their child's medical records to be used,

- all aspects of the trial and require all data collected to date to be excluded from analysis.

A participant may be withdrawn from trial treatment for the following reasons:

- withdrawal of consent for treatment by the parent,
- intolerance to trial medication,
- any alteration in the participant's condition, which, in the opinion of the patient's treating clinician, justifies the discontinuation of the treatment.

In all instances the withdrawal form will be completed on the participant's behalf by the Trial site researcher/clinician based on information provided by the participant's parent. The PI in each site should ensure that a withdrawal form is completed as fully as possible and sent to the OSTRICH TM for every participant that withdraws.

10.2 Loss to Follow up

To minimise loss to follow up, parents who have given permission to be contacted by SMS text messaging will be sent a reminder of their scheduled appointment (where possible).

11 Trial Interventions

11.1 Treatment arms

11.1.1 Active treatment – Oral soluble prednisolone

A 7-day course of oral soluble Prednisolone, as a single daily dose of 20mg for children aged 2-5 years or 30mg for 6-8 year olds. The daily dose stated is the most commonly used dose in previous studies of OME, and is similar to the standard dose for the treatment of other conditions with inflammatory components (such as asthma).

The soluble Prednisolone tablets (5mg) used in this trial are manufactured by Waymade PLC trading as Sovereign Medical. The Marketing Authorisation is PL06464/0914 (see Appendix 1).

Piramal Healthcare UK Limited who have a MHRA Manufacturing Authorisation (MIA IMP 29595) (Appendix 2) will repackage and supply the soluble Prednisolone tablets. Soluble Prednisolone medication will be prescribed by the patient's clinician and dispensed by the Site Pharmacy as described in Section 11.3.

11.1.2 Matched placebo

The placebo used in this trial will be matched for consistency, colour and solubility as well as visually and in its packaging. The placebo is being manufactured, packaged and supplied by Piramal Healthcare UK Limited. Placebo medication will be prescribed by the patient's clinician and dispensed by the Site Pharmacy as described in Section 11.3.

11.2 Supply, packaging, storage and reconciliation of trial medication

Primary bulk manufacturing, labelling and delivery of both soluble Prednisolone and the matching placebo will be performed by Piramal Healthcare UK Limited, who will grant the licence of use of IMP in the UK and also provide primary Qualified Person (QP) release. These products will be manufactured in accordance with Good Manufacturing Practice (GMP).

The manufacturer will label and pack individual Trial Packs, which will be packed into primary (blister packs) and secondary packaging, (cardboard sealed box). The label will state 'for clinical trial use only', and be designed in accordance with Annex 13. Also included on the label will be the name of the Co-Chief Investigators (co-CIs), the Sponsor's details, details for unblinding, the expiry date of the product, the batch number (relating to assembly) and a unique identifier for that pack. As the active treatment is being compared to placebo, to maintain blinding the IMPs will not be labelled for their content on any label on the primary or secondary packaging.

Each Trial Pack will include enough trial medication for a course of 7 days of treatment for one participant. There will be overage in the Trial Pack. Parents will be asked to return the unused medication at the 5 week follow up appointment.

Trial materials will be stored under the conditions specified by the manufacturer (or in the Summary Product Characteristics (SmPCs)/Investigational Medicinal Product Dossier (IMPD) by Piramal Healthcare UK Limited. Trial Packs will be distributed from Piramal Healthcare UK Limited to the Site Pharmacies as required, following a request from Site Pharmacy to the OSTRICH TM. Upon receipt by the Site Pharmacy, all clinical materials will be stored in a designated temperature monitored area within the pharmacy. Site Pharmacies will inform SEWTU when the storage temperature exceeds 27 ^{o}C (25 ^{o}C with a tolerance of an additional 2^{o}C), this will be defined as a temperature excursion. In the event of a temperature excursion, Site Pharmacies will refer to the Pharmacy Manual/IMP Management SOP for procedural details.

All unused or damaged trial medication will be disposed of according to local trial site disposal procedures and logged within the reconciliation form with approval from SEWTU and the trial Sponsor.

11.3 Prescribing and Dispensing Trial medication

The child's treating ENT clinician will complete an OSTRICH Prescription Form (indicating the correct dosage pack) for each child entered into the trial. The prescription will be taken to the local Site Pharmacy for preparation. The Pharmacist will assign the next sequential Trial Pack accordingly and will dispense the Trial Pack to the OSTRICH Trial team member (where possible) or the participant's parent (see section 9.4 for details on allocation of trial medication). A Medication guidance and instructions for use leaflet about the potential IMP (for both active and its placebo medicine) will be given with the Trial pack. Taking of the trial medication should commence ideally on the day after recruitment.

11.4 Dose modification for toxicity

In the event of any observed toxicity (grade 1 and above), modified doses will not be used to continue treatment. The trial medication will be discontinued and the participant will be withdrawn from treatment.

11.5 Interaction with other medications

There is a very small chance of interaction with other drugs. The active steroid is commonly used and has a known safety profile. Most medications that have the potential to interact with the active steroid are very unlikely to be used by meeting the study inclusion criteria. Full details are given in the SmPC for soluble Prednisolone (see Appendix 1). As a precaution, clinicians should refer to the current SmPC or the British National Formulary (BNF) or EMC Medicines.

12 Pharmacovigilance

12.1 Definitions

The following definitions are in accordance with both the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI2004/1031) and the subsequent amendment regulations (SI2006/1938) and the Principles of GCP:

Adverse Event (AE)

Any untoward medical occurrence in a clinical trial participant to whom an IMP has been administered and which does not necessarily have a causal relationship with this

treatment. An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory finding), symptom, or disease.

Adverse Reaction (AR)

Any noxious and unintended response in a clinical trial participant to whom an IMP has been administered, which is related to any dose administered. A "response" to a medicinal product means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

Serious Adverse Event (SAE)

Any adverse event that:

- Results in death
- Is life-threatening*
- Required hospitalisation or prolongation of existing hospitalisation**
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect
- Other medically important condition ***

* Note: The term "life-threatening" in the definition of serious refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

** Note: Hospitalisation is defined as an inpatient admission, regardless of the length of stay, even if the hospitalisation is a precautionary measure, for continued observation. Pre-planned hospitalisation e.g. for pre-existing conditions which have not worsened or elective procedures does not constitute an adverse event.

*** Note: other events that may not result in death are not life-threatening, or do not require hospitalisation may be considered as a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

Serious Adverse Reactions (SARs)

Any SAE occurring in a clinical trial participant for which there is a reasonable possibility that it is related to the IMP at any dose administered.

Suspected Unexpected Serious Adverse Reactions (SUSAR)

These are **SARs** which are classified as '<u>unexpected</u>' i.e. an adverse reaction, the nature and severity of which is not consistent with the applicable product information for prednisolone and matching placebo.

The summary of product characteristics (SmPC) for soluble Prednisolone does not describe any adverse effects associated with short-term use. Although adverse effects are unlikely, dyspepsia and psychiatric reactions (euphoria, depressed mood, insomnia, and behavioural disturbance) may occur following short-term use but will usually resolve on stopping the medication.

Please note: Although the information provided above was comprehensive at the time the current Protocol version was produced, the list of side effects may have been subsequently updated and the site PI should refer to EMC Medicines for updated information.

12.2 Causality

Most AEs and drug reactions that occur in this Trial, whether they are serious or not, will be expected treatment-related toxicities due to the medication used in this Trial.

The assignment of the causality should be made by the Investigator responsible for the care of the participant using the definitions in Table 1 below.

The Chief Investigator (or Clinical Reviewer Delegate) will also be responsible for making an assessment of causality.

12.3 Expectedness

The assessment of whether or not an Adverse Reaction is an expected reaction from the administration of the IMP will be provided by the Chief Investigator (or Clinical Reviewer Delegate), it will not be provided by the Investigator responsible for the care of the participant.

This assessment will be based on the approved Reference Safety Information for the IMP indicated.

Table 1 Definitions of Adverse Events

Relationship	Description
Unrelated	There is no evidence of any causal relationship with the trial/intervention.
Unlikely	There is little evidence to suggest there is a causal relationship with the trial/intervention (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).

Possible	There is some evidence to suggest a causal relationship with the trial/intervention (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definite	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

12.4 Reporting procedures

All SAEs should be reported following randomisation up until the end of the 5 week follow-up period. Depending on the nature of the event, the reporting procedures outlined in this protocol should be followed. Any queries concerning SAE reporting should be directed to SEWTU in the first instance. A flowchart (Figure 2) is given below to illustrate reporting procedures.

12.4.1 Non serious AR/AEs

Potential side effects will be recorded in the participant's diary over the first 5 weeks of their participation. The parent/carer(s) will complete the diary and highlight the severity of any non-serious AR/AEs.

12.4.2 Serious AR/AEs

All SAEs and SUSARs should be reported to the OSTRICH TM at SEWTU within 24 hours of the local site becoming aware of the event. The SAE form asks for the nature of event, date of onset, severity, corrective therapies given, outcomes and causality (i.e. unrelated, unlikely, possible, probably, definitely). The responsible investigator should sign the causality of the event. No assessment of expectedness will be provided by the Investigator responsible for the care of the participant.

An SAE form should be completed for all SAEs and faxed to SEWTU within 24 hours. Additional information should be sent within 5 calendar days if the reaction has not resolved at the time of reporting. SAE reporting and processing procedures will be

included in the training of all research site staff. SAEs should be followed up until resolution.

12.4.3 SUSARs

In the case of serious, unexpected and related adverse events, the staff at the site should:

Complete the SAE case report form and send it immediately (within 24 hours, preferably by fax), signed and dated to SEWTU together with relevant treatment forms and anonymised copies of all relevant investigations.

OR

Contact the OSTRICH TM by phone and then send the completed SAE form to the trial coordination centre, SEWTU by fax within the following 24 hours as above.

SEWTU will notify the MHRA and main Research Ethics Committee (REC) of all SUSARs occurring during the trial according to the following timelines, where day zero is defined as the date the SAE form is initially received at SEWTU:

- SUSARs which are fatal or life-threatening must be reported not later than 7 calendar days after the sponsor is first aware of the reaction. Any additional relevant information must be reported within a further 8 calendar days.
- SUSARs that are not fatal or life-threatening must be reported within 15 calendar days of the sponsor first becoming aware of the reaction.

Local investigators should report any SUSARs and/or SAEs as required by their Local Research and Development Office.

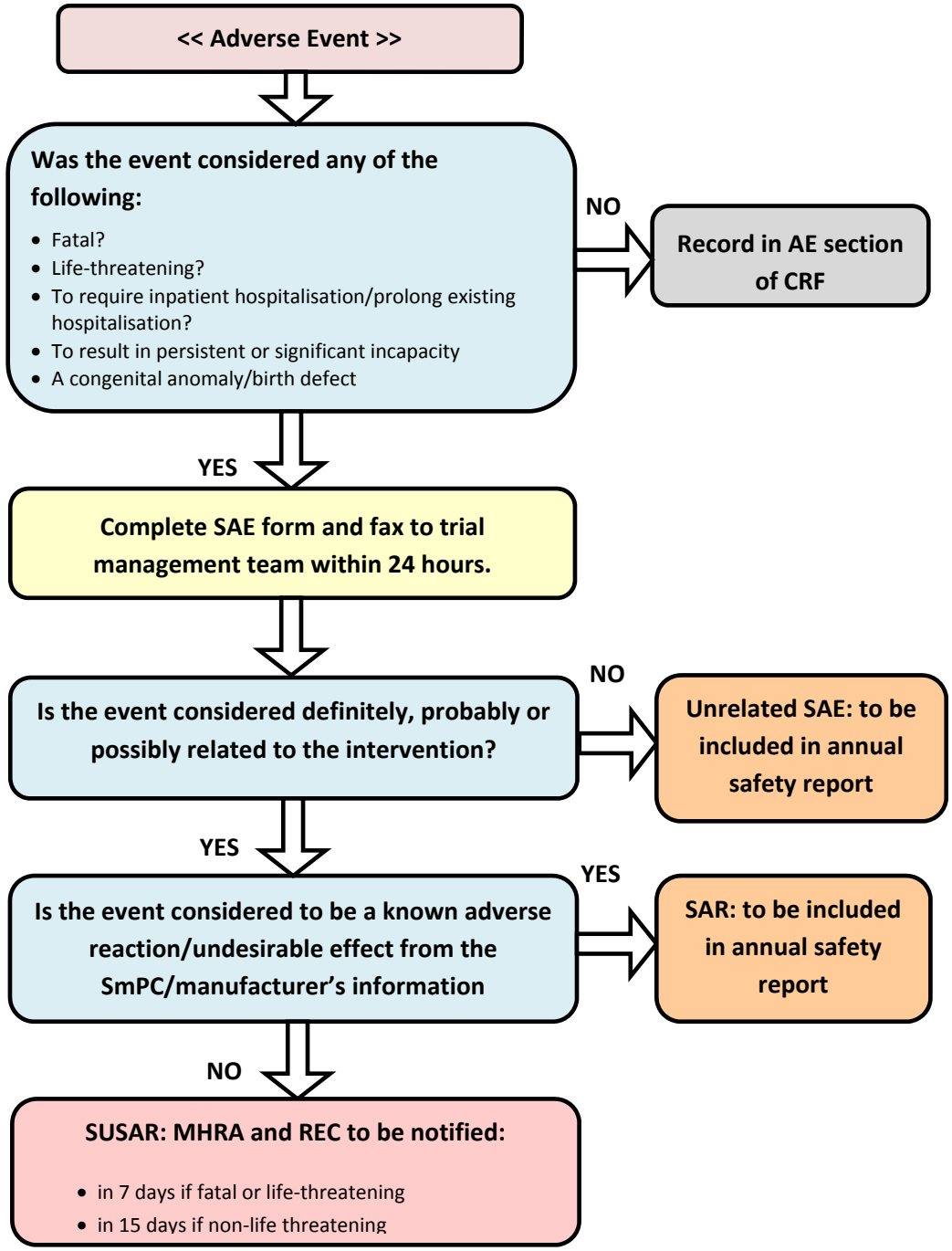
The SEWTU Standard Operating Procedure (SOP) for reporting any SAEs will be used to report to the sponsor, MHRA and REC. An annual Development Safety Update Report (DSUR) will be produced, and will detail all SARs, SUSARs and any other safety information reported (for unblinding in the event of a SUSAR see section 9.4.2).

12.5 Evaluation of SAEs

The local PI should ensure that all SAEs are identified and each one assessed for causality and reported to SEWTU immediately as described in Figure 2. They will be evaluated by staff at SEWTU and one of the CIs (or their delegate) for seriousness, expectedness and causality. Investigator reports of SUSARs will be reviewed immediately and those that are identified and confirmed as SUSARs will be reported to the regulatory authority. In the event of a disagreement between the PI and CI regarding causality of an SAE, the highest relationship (i.e. that closer to definitely

related) will be reported. Expectedness of an SAE should be assessed in relation to the known adverse reactions described in the product characteristics for soluble Prednisolone or the placebo (as provided by the IMP manufacturer, Piramal Healthcare UK Limited).

Figure 2: Flowchart for Adverse Event Reporting Procedures



Contact details for reporting SAEs and SUSARs

Fax: 029 2068 7612,
for attention of OSTRICH TRIAL MANAGER
Please send SAE forms to:
South East Wales Trials Unit (SEWTU)
School of Medicine, Cardiff University
7th floor, Neuadd Meirionnydd
Heath Park
Cardiff, CF14 4YS
Tel: 029 2068 7609 (Mon to Fri 09.00 – 17.00)

13 Trial procedures

13.1 Training of staff

All staff involved in the trial specific procedures (including recruitment/consent, collection of trial data, application of interventions and clinical assessments) will be trained in the required elements of good clinical practice (GCP).

Training materials will be designed for training of trial site staff, including the PI, Research Nurse (RN), and any other designated staff involved in the trial.

The training package will be designed specifically to train different staff groups, depending on the roles and responsibilities of the staff, e.g. trial designated Clinicians, will be trained on trial specific tasks, including assessing eligibility, taking informed consent, IMP management procedures (allocating and dispensing etc) and data collection. Designated staff members will have the responsibility of cascading training and delegating specific Protocol tasks to other trial site staff.

Designated dispensing staff at the trial site will be provided with training on the handling of the trial medication at the start of the trial. Emphasis will be placed on the correct method of storage (including temperature monitoring) of the trial medication, recording medication administration and reconciliation for each patient randomised. Training will also be provided for trial medication stock control at the trial site, which will be monitored by the SEWTU research staff to ensure adequate supply.

14 Data collection / assessment

The schedule for timing, frequency and method of collection of all trial data is summarised in Table 3 below. Assessments will be performed as close as possible to the required time point.

In the event that participants' appointments at the ENT clinic are missed at the proposed time points then SEWTU will coordinate with the trial site staff and the parent of the participant will be contacted by telephone to rearrange the visit as soon as possible. In the event that telephone contact is not successful, then visit reminder letters will be sent to rearrange the appointment.

If parents are unable or unwilling to attend a follow up appointment, they will be asked if they would be willing to complete the Questionnaire booklet that would be sent to them in the post. A Freepost self-addressed envelope will be provided for parents to return their Diary, unused medication and/or Questionnaire booklet. Alternatively, parents will

be given the option of answering a short survey over the telephone, comprising questions extracted from the Diary regarding symptoms (for 5 week follow up if not completing/returning the diary) and quality of life (if not completing and returning a Questionnaire booklet).

Training for completion of trial Case Report Forms (CRFs) will be provided to the appropriate trial site staff prior to trial commencement.

This protocol will use the term 'OSTRICH Nurse' to refer to a clinic nurse, research nurse or clinical studies research officer. Their main role will be to discuss the study with the parent and assist in data collection, and may discuss taking the trial medication with the parent if they are appropriately qualified to do so. The designated OSTRICH Clinician will take informed consent, confirm eligibility, answer any medical questions, and will discuss taking the trial medication (in the absence of a qualified nurse)

14.1 Baseline Assessments

Once informed consent has been obtained the OSTRICH nurse will:

1. Register the participant and their parent to the trial (this will include collecting names and addresses of the participants and their parents),
2. Complete the medical history and baseline CRFs (which will include recording audiology, tympanometry and otoscopy assessments (Table 2).
3. Provide the parent/carer(s) with the trial medication (where possible) or the prescription for the parent/carer(s) to take to the pharmacy, and provide the medication guidance and instructions for use leaflet of the trial medication.
4. Provide the Questionnaire booklet to the parent/carer(s) and complete with the participant (if appropriate).
5. Give the parent/carer(s) a five-week symptom diary and provide them with instructions on diary completion.
6. Arrange next clinic appointment (at week 5) for participant to attend.

The OSTRICH nurse will also advise the parent that there will be further follow up clinic visits at 6 and 12 months.

14.2 Follow-up Assessments

Follow up assessments for all participants will be conducted at week 5 (four weeks post intervention treatment, +1 week window), 6 and 12 months (+/- 2 weeks window).

At the 5 week follow up appointment any unused trial medication will be collected and returned to pharmacy for disposal.

14.2.1 Diary

Parents of children will complete a diary for the first 5 weeks. In the first week this will be completed daily to record treatment adherence. Thereafter, it will be completed weekly for four weeks to record symptoms, adverse events, healthcare consultations, additional medication taken, time off school/nursery and parental time off work.

14.2.2 Clinical Assessments

The following hearing assessment will be measured at 5 weeks post randomisation (four weeks post treatment), 6 months and 12 months:

Table 2: Clinical Measurements

Measurement	**Outcome**
Audiometry	Hearing in each ear by pure tone audiometry, ear specific insert visual reinforcement audiometry (VRA) or ear specific play audiometry) or in both ears together by soundfield VRA or soundfield performance/play audiometry).
Tympanometry *(using calibrated standardised tympanometers and modified Jerger classification Type B and C considered abnormal)*	Presence of middle ear effusion in each ear
Otoscopy	Appearance of tympanic membrane

In current practice, the recommended standard methods to assess hearing thresholds are ear specific pure tone audiometry (PTA) at 0.5, 1, 2 and 4 kHz in children aged 3 or more, and soundfield visual reinforcement audiometry (VRA) in children under 3. However, equally those under 3 years of age may comply with PTA. Therefore, we recommend that the Audiologist/ Clinician use their judgement on the most appropriate method of assessment for the child, and where possible maintain that method for subsequent follow ups.

We are aware that ear specific VRA through the use of insert earphones is considered 'gold standard' practice, but believe that soundfield VRA will provide a reasonable assessment of the child's level of hearing, and will ensure the feasibility of the trial in a range of research sites.

Although the follow-up of participants will be continued for 12 months, after the 5 week assessment all participants will resume to 'usual care' and all treatment decisions will be made by their parents in consultation with their ENT clinician.

14.2.3 Functional Health Status and Quality of life

Functional Health Status (via OM8-30) and health-related quality of life (via Pediatric Quality of Life Inventory (PedsQL) and Health Utilities Index Mark 3 (HUI 3)) will be assessed at the end of week 5 and at 6 and 12 months, through parent completed questionnaires.

14.2.4 Healthcare Resource Usage

A record of the healthcare resource usage will be collected for participants at the end of week 5 and at 6 and 12 months following treatment. This enables assessment of any use of NHS resources, (including General Practitioner (GP) and practice nurse consultations, procedures, investigations, hospital appointments, A&E attendances and any hospital inpatient admissions).

14.2.5 Medical Records search

Data will be extracted from secondary care medical records and where possible primary care medical records for each participant for the 12-month period following recruitment. Linkage of trial participants' identifiable data (NHS number, date of birth, gender, address and postcode etc) with their primary and secondary care medical records will be conducted using the Secure Anonymised Information Linkage (SAIL) Databank. The SAIL databank is a large scale data warehouse which links together person-based data. For secondary care records the Patient Episode Database for Wales (PEDW) and for primary healthcare records the GP records will both be accessed through SAIL at 12 months following recruitment of their last participant. The record search will be used to identify secondary healthcare consultations and primary healthcare consultations (where possible), including any subsequent treatments.

If recruiting in England the Clinical Practice Research Datalink (CPRD) will be used to link to and access secondary care data from Hospital Episode Statistics (HES) and primary care medical records.

Table 3: Summary of Data Collection

Data Type	Baseline Evaluation	Follow Up Period		
		5 Weeks	6 months	12 months
	Clinic Visit	Clinic Visit / Parent Diary	Clinic Visit /Questionnaires	Clinic Visit /Questionnaires
1. Demographics	X			
2. Medical History	X			
3. Audiometry	X	X	X	X
4. Tympanometry	X	X	X	X
5. Otoscopy	X	X	X	X
6. Medication use		X		
7. Grommet Surgery Required		X	X	X
8. Daily symptoms		X		
9. Adverse effects		X		
10. Resource use		X	X	X
11. Functional health status (OM8-30, HUI3)	X	X	X	X
12. Health related Quality of Life (PedsQL)	X	X	X	X
13. SAEs	I< ----------as required ---------- >I			
14. Withdrawals	I<---------- as required ---------- >I			

15 Statistical considerations

15.1 Randomisation

A list of allocations (steroid or placebo) will be randomly generated by the TS using random permuted blocks that are stratified. Computer generated random numbers will be produced to select a block of allocations from the set of all possible permutations of allocations (on a 1:1 ratio) given a particular block size before the trial begins.

15.2 Primary Outcome Measure

Acceptable hearing at five weeks from randomisation (four weeks after conclusion of treatment), where acceptable hearing is defined as 'less than or equal to 20 dBHL' averaged within the frequencies of 0.5, 1, 2 and 4 kHz in at least one ear in children assessed by PTA, ear specific insert VRA or ear specific play audiometry, and 'less than or equal to 25 dBHL' averaged within the frequencies of 0.5, 1, 2 and 4 KHz in children assessed by soundfield VRA or soundfield performance/play audiometry. These thresholds are based on national guidelines[23]. The 5-week follow-up will provide evidence of the short-term effectiveness of the intervention. Oral steroids are likely to have their effect within the first few weeks, and most of the existing evidence is for effect at 4-6 weeks. This is, therefore, the time point at which the maximum effect is expected.

15.3 Secondary Outcome Measures

- Satisfactory hearing at 6, and 12 months, measured as above,
- Tympanometry (using calibrated standardised tympanometers and modified Jerger classification Types A, B and C),
- Otoscopic findings,
- Healthcare consultations related to OME, and other resource use,
- Grommet surgery at 6, and 12 months,
- Adverse effects,
- Symptoms (reported by parent and/or child),
- Functional health status (OM8-30 and HUI3),
- Health related quality of life (PedsQL),
- Short and longer term cost effectiveness.

15.4 Sample size

The sample size calculation is based on demonstrating a change in the rate of resolution of hearing loss at 5 weeks post randomisation (four weeks post completion of treatment)

from 20% in the control group to 35% in the intervention group. OME resolves spontaneously in a high proportion of children, and some studies have found a significantly higher rate of spontaneous resolution. For example, Williamson *et al*. found a resolution rate in their control group of 47%[14]. However, we anticipate a lower spontaneous rate of resolution both because we will only include children who have been symptomatic for at least three months, and because we are recruiting children in a secondary care setting, where a more severe spectrum of illness can be anticipated. The Cochrane review of steroids for OME reported a ratio of proportions for resolution of OME at 2 weeks of 3.80 (95% CI=0.93 to 15.52). In the 5 studies in the Cochrane review of oral steroids vs. placebo, overall there was a 23% recovery rate in the placebo plus antibiotic group and a 47% recovery rate in the oral steroid plus antibiotic group, a 24% difference (antibiotic on their own are ineffective)[12]. We have selected a conservative estimate of 1.75 for our effect size (ratio of proportions) because we believe that a 15% absolute increase in the rate of resolution at 5 weeks would represent a clinically meaningful result that would result in a meaningful reduction in unnecessary operations with a related meaningful saving in cost for the NHS. In order to demonstrate a difference between 20% and 35% with an alpha of 0.05 and 80% power we will need 302 participants (nQuery software version 4.0). We will recruit 380 to allow for a 20% loss to follow up at one year. Although our primary outcome data will be gathered at 5 weeks, we believe that it is important to be able to assess long-term outcomes, and therefore, want to ensure that we will have sufficient power for longer-term follow assessments.

16 Analysis

16.1 Main analysis

The analysis and presentation of this randomised trial will be in accordance with CONSORT guidelines, with the primary comparative analyses being conducted on an intention-to-treat (ITT) basis and due emphasis placed on confidence intervals for the between-arm comparisons. Descriptive statistics of demographic and outcome measures will be used to ascertain any marked imbalance between the two arms at baseline. Where variables exhibit marked imbalance at baseline, primary analyses will be repeated and adjustments made to assess impact on estimates. Further analysis will be provided in the Statistical Analysis Plan.

16.2 Primary outcome analysis

The primary comparative analyses (proportion of children with acceptable hearing at the 5 weeks post randomisation follow-up appointment) will employ logistic regression to investigate differences between the two arms, adjusting for site. Comparisons will be presented as ratio of proportions, odds ratios, 95% confidence intervals and p-values.

16.3 Analysis of secondary outcomes

Secondary outcomes with a binary outcome (present/absent) such as satisfactory hearing and presence of effusion will employ repeated measures logistic regression to investigate differences between the two trial arms and over time (6 and 12 months follow-up). For continuous secondary outcomes such as PedsQL, and OM8-30 scores, repeated measures linear regression models (using transformations as necessary) will be used to investigate differences between the two trial arms and over time (baseline, 5 weeks, 6 and 12 months). The duration between the start and the resolution of the symptoms will be calculated and group differences examined using Cox regression analysis to calculate hazard ratios for referral, together with 95% confidence intervals.

The association between outcomes that are measured by more than one method (e.g. such as hearing measured by audiometry and parental report and resolution of effusion as measured by otoscopy and tympanometry) will be assessed using linear or logistic regression depending on the nature of the data. For all analyses, parameter estimates/odds ratios will be shown alongside 95% confidence intervals and p-values.

A number of outcomes will be calculated from the parents' diary for the first 5 weeks such as total time off school/nursery and work (days), and number of healthcare consultations. These will be analysed using Poisson regression to investigate differences between the two trial arms.

Previous researchers have mapped OM8-30 scores to utility values on the HUI-3 scale. As we are measuring both OM8-30 and HUI-3, we will use this opportunity to evaluate the generalizability of the existing mapping. We will do this by correlating the mapped utility values on the HUI-3 scale (obtained via the mapping formula from the OM8-30 facet scores) with the newly acquired HUI-3 scores.

16.4 Sub-group and interim analysis

Possible confounders such as age and history of atopy, and relevant interaction terms will be entered into the primary regression analyses for each of the outcomes in order to conduct pre-specified subgroup analyses. These subgroups will be defined in advance of any analysis based on best available evidence. Since the Trial is powered to detect overall differences between the groups rather than interactions of this kind, the results

of these exploratory analyses will be presented using confidence intervals as well as p-values. No interim analyses are planned.

16.5 Cost effectiveness analysis

The cost-effectiveness analysis will be conducted from the perspective of the UK NHS and Personal Social Services and also consider a broader partial societal perspective, encompassing impact on patients and their families. The cost-effectiveness component will have two time durations: a within-trial assessment and a longer-term time horizon based on decision-analytic modelling and populated from parameter estimates derived from the Trial and from information from literature sources relating to long-term effects of hearing difficulties in children. These time periods offer a longer duration than previous studies and will be used, alongside other sources, to arrive at more meaningful estimates of cost-effectiveness.

The costs of the course of oral corticosteroid will be computed and combined with differences in costs between intervention and control groups to determine overall costs associated with the intervention. The resource utilisation of both groups (consultations, medications, operations, equipment, etc.) and treatments associated with AEs, will be assessed through the completion of self-completed questionnaires at baseline, at 5 weeks, 6 months and 12 months and translated into costs using appropriate published unit costs (e.g. Curtis, 2010)[24]. In addition, questionnaire responses will be validated through an interrogation of secondary care and primary care records where possible at 12 months.

The difference in overall costs between groups will be compared with differences in outcomes, as specified above, and including Quality-adjusted Life Years (QALYs). QALYs will be computed from PedsQL and the Health Utilities Index Mark 3 (HUI 3) and from utilities derived from mapping responses to the OM8-30 otitis media questionnaire[25].

A series of one-way sensitivity analyses will be conducted to assess the impact of parameter variation on baseline estimates of the cost-effectiveness ratios and a probabilistic sensitivity analysis undertaken to determine the extent to which the intervention can be regarded as representing value for money.

Mapping OM8-30 scores to HUI-3 scores

Mapping disease-specific scores to generic utility scales is a standard approach. Obviously, if there is some relatively strong correlation between a specific health status measure and a generic health-related QoL measure, the availability of a mapping creates the possibility to estimate on a standard generic scale, the (usually more diluted) effect of a treatment on overall quality of life. This can be done while retaining the good

properties (usually, brevity, precision, reliability and respondent-relevance) of the specific disease-based measure. Mappings are applicable in future studies of all types that may not have the resources of a centrally funded trial to also acquire generic measures, and also to bring past studies into systematic review on a universal metric.

OM8-30 scores have previously been mapped to HUI-3 utilities with reasonably small mean absolute errors (MAEs)[25]. We plan on testing the generalisability of the existing mapping by correlating the mapped utility values on the HUI-3 scale (obtained via the mapping formula from the OM8-30 facet scores) with the newly acquired HUI-3 scores (all measures obtained by parent proxy). We plan on working with Haggard (originator of the OM8-30 and involved in the previous mapping exercise) to undertake the necessary analyses. It is hoped that this work will contribute to the development and validation of a short form of the OM8-30 (the Q-14), which is likely to become a widespread standard in ENT and paediatrics.

16.6 Data storage & retention

Essential trial documentation and source data will be archived in line with Cardiff University's Research Governance Framework Regulations (RGFR) for clinical research and the Cardiff University Archiving SOP (CU/08/S22). As the trial involves participants under the age of 18, all data will be kept until the youngest participant has reached the age of 21. This data will be stored confidentially on password-protected servers maintained on the Cardiff University Network.

Electronic data will be stored on fire-walled University computers, and only accessible to researchers involved in the trial. All procedures for data storage, processing and management will be in compliance with the Data Protection Act 1998. All paper records will be stored in a locked filing cabinet, with keys available only to the trial management team. The TS will carry out analysis. All essential documents generated by the Trial will be kept in the Trial Master File (TMF).

17 Qualitative Sub-study

17.1 Aims of sub-study

The aim of the sub-study is to describe parents' understanding and perceptions regarding treatment options for glue ear before and after they have had a consultation with an ENT specialist.

17.2 Sub-study methods

Design: Qualitative interview study. Individual interviews have been chosen as an effective way to explore the perception of parents of children with OME regarding different treatment modalities. Qualitative interviews help observe and record a participant's unique perspective or experience relating to a particular issue. In addition, more complex, in-depth data can be collected and based on responses to primary questions, prompts can be offered for subjects to elaborate on. Interviews will be conducted at baseline, after parents have agreed to take part in the OSTRICH study and at follow-up, after five weeks.

Participants: 20-30 parents of children who have agreed to participate in the OSTRICH main study and agree to participate in the sub-study.

Participant identification, recruitment and consent procedures: A medical student working with the OSTRICH study team will attend the ENT clinic on days when children are being recruited into the study. On these days, parents agreeing to participate in OSTRICH will be invited to participate in an additional optional interview in relation to this aspect of the study. The invitation will be made by their treating clinician or by the research nurse. Those who express an interest will be approached by the medical student, provided with further verbal information about the sub-study and provided with a written participant information sheet about the sub-study, and be invited to participate. If they are willing to participate they will be asked to sign a consent form prior to the interview. Participants will be informed that they can change their mind and withdraw consent at any time.

Interview procedures: The interviews will be conducted in a quiet, private environment and will be audio recorded and transcribed. The interview should last no longer than 30 minutes.

Analysis: The transcripts will be transcribed verbatim and analysed using a thematic approach. A thematic coding framework will be developed and discussed amongst the research team. The analysis will be supported by the use of computer-assisted qualitative analysis software (NVIVO).

Data protection: No patient data will be accessed or used in the course of the study. Audio recordings will be kept on secure a university network and transcriptions will be anonymised. All personal data will be kept confidential and secure.

Dissemination: The results of this sub-study will be used to form the basis of a report completed by the medical student as part of a 'student selected component' and will form the basis of a scientific article which will be submitted for publication. The results

may also be presented at scientific meetings. No identifiable data will be included in any research outputs.

18 Trial closure

For the purpose of regulatory and ethical requirements the end of the Trial is defined as the end of the follow-up period of the last participants.

19 Regulatory issues

19.1 Clinical Trials Authorisation

The sponsor, Cardiff University, will determine the level of monitoring required after assessing risk together with SEWTU. The trial will be conducted to the Principles of GCP and the applicable UK Regulations governing clinical trials. This trial had a European Clinical Trials Database (EudraCT) number (2012-005123-32). A Clinical Trials Authorisation (CTA) from the UK Competent Authority: Medicines and Healthcare products Regulatory Agency (MHRA) will be obtained. We will meet all regulatory requirements to report AEs, in particular Suspected Unexpected Serious Adverse Reactions (SUSARs). The TM will report SUSARS to the MHRA within 7 calendar days for life-threatening and 15 calendar days for non-life-threatening. Roles and responsibilities will be set ahead of the Trial commencing. Investigational Medicinal Products (IMPs) will be manufactured according to Good Manufacturing Practice (GMP) by the manufacturer and supplier of the branded product and placebo by the supplier of the branded products and placebo manufacturer, labelled according to Annex 13 and supervised and distributed by a Qualified Person (QP). All the staff involved in the Trial will be GCP trained and drug accountability logs maintained.

19.2 Ethical Approval and Research Governance

The Trial will be conducted in accordance with the recommendations for physicians involved in research on human participants adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

This Trial Protocol will be submitted to a Research Ethics Committee (REC) recognised by the United Kingdom Ethics Committee Authority (UKECA) for review and approval. A favourable ethical opinion will be obtained from the REC before commencement of any trial procedures (including recruitment of participants).

Research governance approvals will be sought from the respective NHS Health Boards in Wales. Clinical Trial Authorisation will be sought from the Medicines and Healthcare products Regulatory Agency.

All substantial protocol amendments must be approved by the REC responsible for the trial, in addition to approval by NHS Research and Development (R&D) (and MHRA approval if applicable to the amendment). Minor amendments will not require prior approval by the REC.

If the trial is stopped due to adverse events or an urgent safety measure it will not be recommenced without reference to the REC responsible for the trial.

The outcome of the trial (e.g. completed) will be reported to the REC responsible for the trial within 90 calendar days of trial closure. In the event of the trial being prematurely terminated a report will be submitted to the REC responsible for the trial within 15 calendar days.

A summary of the Clinical Trial Report will be submitted to the REC responsible for the trial within one year of completion of trial closure.

19.3 Ethical conduct of the trial

The CI and the Co-Investigators shall be responsible for ensuring that the clinical trial is performed in accordance with the following:

- Declaration of Helsinki (Seoul, 2008).
- Principles of GCP.
- The Medicines for Human Use (Clinical Trials) Regulations 2004 [26] (Statutory Instrument 2004 No. 1031) as amended by the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 (Statutory Instrument 2006 No. 1928 and No. 2984) and Amended Regulations 2008 (Statutory Instrument 2008 No. 941).
- Research Governance Framework for Health and Social Care (RGFR) (Welsh Assembly Government 2nd Edition, September 2009 and Department of Health 2nd Edition, July 2005).

19.4 Risks and anticipated benefits for trial participants

Short courses of oral steroids (Prednisolone) are currently widely used in the NHS and worldwide for the management of acute asthma in children and have an excellent safety profile. Although long-term or frequent courses of oral steroids are associated with important adverse effects, repeated short courses of Prednisolone (up to 4 per year) in children with asthma have been shown to be relatively safe and not associated with any lasting effects on bone metabolism or mineralization or adrenal function[22]. There are

small risks of side effects (such as gastrointestinal disturbance or behavioural effects) from the Trial medication, which will be explained to participating parents and children (where appropriate).

The potential benefits for participants include satisfactory resolution of hearing, and the functional, psychological, and social benefits associated with resolution of satisfactory hearing, and avoidance of surgery and hearing aids. Potential benefits for society include confirmation of the effectiveness, safety, and cost-effectiveness of a simple, cheap intervention that could result in important health benefits for a common childhood condition and a significant reduction in the most common surgical procedure conducted in childhood.

At the time of enrolment, parents will be informed that if their child enters the trial they will not be able to have grommet surgery until after their initial follow-up assessment (at 5 weeks), unless they withdraw from the trial. However, parents in both treatment arms will be given the option of placing their child on the waiting list for grommet surgery at the time of trial registration as advised by their ENT clinician. At 5 weeks, children who have not achieved acceptable hearing will be offered surgery. Therefore, most participants will not be disadvantaged, in terms of waiting time for surgery, by participating in the trial. Only those children who do not achieve acceptable hearing by 5 weeks and who are attending a clinic where the waiting time for surgery is less than 5 weeks, will have their waiting time extended, and then only by a maximum of 5 weeks. At the present time, it is highly unusual for children to receive ventilation tube insertion within five weeks of being listed for surgery. Although we will continue to follow-up participants for 12 months, after the 5 week assessment all participants will resume to their 'usual care' and all treatment decisions will be made by their parents, in consultation with their clinician(s).

19.5 Consent

Informed consent will be taken by only suitably qualified, experienced and trained personnel in accordance to the principles of GCP on taking consent and before any trial related procedures are undertaken. The trial participants are young children (2 years to 8 years of age), and the parent/guardians(s) will be asked to give written informed consent on behalf of their child for their child to take part in the trial.

We will also seek to gain assent from the older children where deemed appropriate by the OSTRICH team member. Age appropriate pictorial information sheets will be available for the children.

19.6 Confidentiality

The PIs and the OSTRICH research team will preserve the confidentiality of participants in accordance with the Data Protection Act 1998. All data will be handled according to the principles of the Data Protection Act, especially for sensitive and personal data. Data will be anonymised and stored on a password-protected computer located in secure University buildings and be appropriately backed up. Any data transfer across participant organisations will be closely monitored by a designated member of the trial team. A privacy risk assessment will proactively identify and ameliorate risks of breaches of confidentiality and clearly designate the named individuals who will be allowed access to identifiable and unblinded information. Published outcomes of the trial will not enable identification of the individual participants. All data will be retained until the youngest participant has reached the age of 21 in line with Cardiff University's procedures.

19.7 Indemnity

Cardiff University will provide indemnity and compensation in the event of a claim by, and on behalf of participants, for negligent harm as a result of the trial design and/or in respect of the Protocol authors/research team. Cardiff University will not provide compensation for non-negligent harm.

All participants will be recruited at NHS sites and therefore the NHS indemnity scheme/NHS professional indemnity will apply with respect to claims arising from harm to participants at site management organisations.

19.8 Trial sponsorship

Cardiff University will act as sponsor for the trial. Delegated responsibilities will be assigned to the NHS Health Boards and collaborating institutes taking part in this trial.

19.9 Funding

This trial is funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme (11/01/26).

19.10 Audits & inspections

The trial is open to inspection by the NIHR HTA as the funding organisation. The trial may also be subject to inspection and audit by Cardiff University under their remit as sponsor. As this trial is classified as a Clinical Trial of Investigational Medicinal Products (CTIMP), it may also be subject to inspection by the MHRA.

20 Trial management

20.1 Project Team (PT)

This group will consist of members of the trial team involved in the day-to-day conduct of the trial, and will include the Chief Investigators (CIs), Principal investigators, (PIs) Trial Manager (TM), Trial Statistician (TS), Data Manager (DM) and Trial Administrator (TA). The group will normally meet weekly to discuss the day-to-day issues that arise from the trial. Important discussions will be relayed to the Trial Management Group (TMG) to for a final decision.

20.2 Trial Management Group (TMG)

The TMG will consist of the CIs, Co-Applicants, Collaborators, TM, DM, TS and TA.

The role of the TMG will be to help set up the trial by providing specialist advice, input to and comment on trial procedures and documents (information sheets, Protocol, etc.). They will also advise on the promotion and running of the trial and deal with any issues that arise. The group will normally meet monthly throughout the course of the trial. TMG members will be required to sign up to the remit and conditions as set out in the TMG Charter which will be filed in the Trial Master File (TMF).

20.3 Trial Steering Committee (TSC)

A TSC, consisting of an independent chair, and two other independent members including a patient representative, will meet at least annually. The first meeting will be before the trial commences to review the Protocol and arrange the timelines for the subsequent meetings. If necessary, additional/more frequent meetings may occur. The TM and TS will attend as observers. The TSC will provide overall supervision for the trial and provide advice through its independent chair. The ultimate decision for the continuation of the trial lies with the TSC.

TSC members will be required to sign up to the remit and conditions as set out in the TSC Charter which will be filed in the TMF.

20.4 Independent Data Monitoring Committee (IDMC)

In order to monitor accumulating data on safety and any trial intervention benefit, an IDMC will be established. The Committee will consist of an independent chair and two/three other independent members. The first meeting will take place before the trial commences in order to review the Protocol and agree on timelines for interim analyses to take place. The main role of the IDMC is to review the data periodically and makes recommendations to the TSC.

IDMC members will be required to sign up to the remit and conditions as set out in the IDMC Charter which will be filed in the TMF.

21 Data monitoring & quality assurance

Regular monitoring will be performed according to the principles of GCP. Data will be evaluated for compliance with the Protocol and accuracy in relation to source documents. Following written SOPs, the monitors will verify that the OSTRICH trial is conducted and data are generated, documented and reported in compliance with the Protocol, GCP and the applicable regulatory requirements.

22 Publication policy

All publications and presentations relating to the OSTRICH trial will be authorised by the TMG and will be in accordance with the trial's publication policy. In addition to the required final report and monograph for the HTA Programme, we will publish the main trial results in international peer-reviewed journals and present at national and international scientific meetings. With the assistance of our collaborators and lay representatives we will disseminate the trial findings to a wide NHS and general audience and vigorously promote uptake of the trial results into clinical care. This will include presentations at meetings and written executive summaries for key stakeholder groups such as Primary Care Trusts and General Practices, Royal Colleges, Medical Schools, and relevant patient groups.

23 Milestones

The OSTRICH trial is a 3 year trial, with the following project timetable:

Months	**Activity**
0 – 6	Trial set-up • Hire & train staff • Develop & print Trial materials • Design & validate Trial database • Source and package pharmaceuticals • Recruit and train centres
7 – 18	Recruit participants
8 – 30	Participant follow-up
19 – 36	Data cleaning, analyses, reports, dissemination

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25 Appendices

Appendix 1 - SmPC for soluble Prednisolone

PRODUCT SUMMARY

1. NAME OF THE MEDICINAL PRODUCT

Prednesol Tablets 5mg
Soluble Prednisolone Tablets 5mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Small, pink, soluble tablets engraved ‘Pred 5 Sov’ on one side and scored on the reverse. Each tablet contains 5mg prednisolone as the sodium phosphate ester.

3. PHARMACEUTICAL FORM

Tablet.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

A wide variety of diseases may sometimes require corticosteroid therapy. Some of the principal indications are:

bronchial asthma, severe hypersensitivity reactions, anaphylaxis; rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, mixed connective tissue disease (excluding systemic sclerosis), polyarteritis nodosa;

inflammatory skin disorders, including pemphigus vulgaris, bullous pemphigoid and pyoderma gangrenosum;

minimal change nephrotic syndrome, acute interstitial nephritis;

ulcerative colitis, Crohn’s disease; sarcoidosis;

rheumatic carditis;

haemolytic anaemia (autoimmune), acute lymphoblastic and chronic lymphocytic leukaemia, malignant lymphoma, multiple myeloma, idiopathic thrombocytopenic purpura;

immunosuppression in transplantation.

4.2. Posology and Method of Administration

Prednesol/Soluble Prednisolone Tablets are best taken dissolved in water, but they can be swallowed whole without difficulty.

The lowest dosage that will produce an acceptable result should be used (See precautions section); when it is possible to reduce the dosage, this must be accomplished by stages. During prolonged therapy any intercurrent illness, trauma or surgical procedure will require a temporary increase in dosage; if corticosteroids have been stopped following prolonged therapy they may need to be temporarily re-introduced.

Adult: The dose used will depend upon the disease, its severity, and the clinical response obtained. The following regimens are for guidance only. Divided dosage is usually employed.

Short-term treatment: 20 to 30mg daily for the first few days, subsequently reducing the daily dosage by 2.5 or 5mg every two to five days, depending upon the response.

Rheumatoid arthritis: 7.5 to 10mg daily. For maintenance therapy the lowest effective dosage is used.

Most other conditions: 10 to 100mg daily for one to three weeks, then reducing to the minimum effective dosage.

Children: Fractions of the adult dosage may be used (e.g. 75% at 12 years, 50% at 7 years and 25% at 1 year) but clinical factors must be given due weight.

Soluble Prednisolone Tablets may be given early in the treatment of acute asthma
attacks in children. For children over 5 years use a dose of 30-40mg prednisolone.
For children aged 2-5 years use a dose of 20mg prednisolone. Those already receiving maintenance steroid tablets should receive 2 mg/kg prednisolone up to a maximum dose of 60mg. The dose of prednisolone may be repeated for children who vomit; but intravenous steroids should be considered in children who are unable to retain orally ingested medication. Treatment for up to three days is usually sufficient, but the length of course should be tailored to the number of days necessary to bring about recovery. There is no need to taper the dose at the end of treatment.

For children under 2 years, Soluble Prednisolone Tablets can be used early in the management of moderate to severe episodes of acute asthma in the hospital setting, at a dose of 10mg for up to three days.

4.3. Contra-Indications

Systemic infections, unless specific anti-infective therapy is employed. Live virus immunisation. Hypersensitivity to any component of the tablets.

4.4 Special warnings and precautions for use

In patients who have received more than physiological doses of systemic corticosteroids (approximately 7.5 mg prednisolone or equivalent) for greater than 3 weeks, withdrawal should not be abrupt. How dose reduction should be carried out depends largely on whether the disease is likely to relapse as the dose of systemic corticosteroids is reduced. Clinical assessment of disease activity may be needed during withdrawal. If the disease is unlikely to relapse on withdrawal of systemic corticosteroids but there is uncertainty about HPA suppression, the dose of systemic corticosteroid may be reduced rapidly to physiological doses. Once a daily dose equivalent to 7.5 mg prednisolone is reached, dose reduction should be slower to allow the HPA axis to recover.

Abrupt withdrawal of systemic corticosteroid treatment, which has continued up to 3 weeks is appropriate if it is considered that the disease is unlikely to relapse. Abrupt withdrawal of doses of up to 40 mg daily of prednisolone, or equivalent for 3 weeks is unlikely to lead to clinically relevant HPA axis suppression, in the majority of patients. In the following patient groups, gradual withdrawal of systemic corticosteroid therapy should be *considered* even after courses lasting 3 weeks or less:

- Patients who have had repeated courses of systemic corticosteroids, particularly if taken for greater than 3 weeks
- When a short course has been prescribed within one year of cessation of long-term therapy (months or years),
- Patients who may have reasons for adrenocortical insufficiency other than exogenous corticosteroid therapy, been stopped following prolonged therapy they may need to be temporarily reintroduced.
- Patients receiving doses of systemic corticosteroid greater than 40mg daily of prednisolone (or equivalent),
- Patients repeatedly taking doses in the evening.

Patients should carry 'Steroid treatment' cards which give clear guidance on the precautions to be taken to minimise risk and which provide details of prescriber, drug, dosage and the duration of treatment.

Adrenal cortical atrophy develops during prolonged therapy and may persist for years after stopping treatment. Withdrawal of corticosteroids after prolonged therapy must therefore always be gradual to avoid acute adrenal insufficiency, being tapered off over weeks or months according to the dose and duration of treatment. During prolonged therapy any intercurrent illness, trauma or surgical procedure will require a temporary increase in dosage; if

corticosteroids have been stopped following prolonged therapy they may need to be temporarily re-introduced.

Suppression of the HPA axis and other undesirable effects may be minimised by using the lowest effective dose for the minimum period, and by administering the daily requirement as a single morning dose or whenever possible as a single morning dose on alternate days. Frequent patient review is required to appropriately titrate the dose against disease activity. (See dosage section).

Anti-inflammatory/immunosuppressive effects and infection
Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy. Discontinuation of corticosteroids may result in clinical remission.

Chronic immunosupression (e.g. in the setting of organ transplantation), has been associated with an increased risk of malignancy.

Suppression of the inflammatory response and immune function increases the susceptibility to infections and their severity. The resultant opportunistic infections may be fatal. The clinical presentation may often be atypical and serious infections such as septicaemia and tuberculosis may be masked and may reach an advanced stage before being recognised.

Chickenpox is of particular concern since this normally minor illness may be fatal in immunosuppressed patients. Patients without a definite history of chickenpox should be advised to avoid close personal contact with chickenpox or herpes zoster and if exposed they should seek urgent medical attention. If the patient is a child parents must be given the above advice. Passive immunisation with varicella zoster immunoglobulin (VZIG) is needed by exposed non-immune patients who are receiving systemic corticosteroids or who have used them within the previous 3 months; this should be given within 10 days of exposure to chickenpox. If a diagnosis of chickenpox is confirmed, the illness warrants specialist care and urgent treatment.
Corticosteroids should not be stopped and the dose may need to be increased.

Patients should be advised to take particular care to avoid exposure to measles and to seek immediate advice if exposure occurs. Prophylaxis with intramuscular normal immunoglobulin may be needed.

Live vaccines should not be given to individuals with impaired immune responsiveness caused by high doses of corticosteroids. The antibody response to other vaccines may be diminished.

Because of the possibility of fluid retention, care must be taken when corticosteroids are administered to patients with renal insufficiency or hypertension or congestive heart failure.

Corticosteroids may worsen diabetes mellitus, osteoporosis, hypertension, glaucoma and epilepsy and therefore patients with these conditions or a family history of them should be monitored frequently.

Care is required and frequent patient monitoring necessary where there is a history of severe affective disorders (especially a previous history of steroid psychosis), previous steroid myopathy, peptic ulceration, hypothyroidism, recent myocardial infarction or patients with a history of tuberculosis.

In patients with liver failure, blood levels of corticosteroid may be increased, as with other drugs which are metabolised in the liver. Frequent patient monitoring is therefore necessary.

Use in Children: Corticosteroids cause dose-related growth retardation in infancy, childhood and adolescence, which may be irreversible.

Use in the Elderly: The common adverse effects of systemic corticosteroids may be associated with more serious consequences in old age, especially osteoporosis, hypertension, hypokalaemia, diabetes, susceptibility to infection and thinning of the skin. Close clinical supervision is required to avoid life-threatening reactions.

[1]Patients/and or carers should be warned that potentially severe psychiatric adverse reactions may occur with systemic steroids (see Section 4.8 Undesirable effects). Symptoms typically emerge within a few days or weeks of starting the treatment. Risks may be higher with high doses/systemic exposure (see also Section 4.5 Interaction with other medicinal products and other forms of interaction), although dose levels do not allow prediction of the onset, type, severity or duration of reactions. Most adverse reactions resolve after either dose reduction or withdrawal of the medicine, although specific treatment may be necessary. Patients/carers should be encouraged to seek medical advice if worrying psychological symptoms develop, especially if depressed mood or suicidal ideation is suspected. Patients/carers should also be alert to possible psychiatric disturbances that may occur either during or immediately after dose tapering/withdrawal of systemic steroids, although such reactions have been reported infrequently.

Particular care is required when considering the use of systemic corticosteroids in patients with existing or a previous history of severe affective disorders in themselves or in their first degree relatives. These would include depressive or manic-depressive illness and previous steroid psychosis.

4.5. Interactions with other Medicinal Products and other Forms of Interaction

[1] PL06464/0914-0028; 01/04/2008

Rifampicin, rifabutin, carbamazepine, phenobarbitone, phenytoin, primidone, ephedrine and aminoglutethimide enhance the metabolism of corticosteroids and its therapeutic effects may be reduced.

Mifepristone may reduce the effect of corticosteroids for 3-4 days.

Erythromycin and ketoconazole may inhibit the metabolism of some corticosteroids.

Ciclosporin increases plasma concentration of prednisolone. The same effect is possible with ritonavir.
Oestrogens and other oral contraceptives may potentiate the effects of glucocorticoids and dosage adjustments may be required if oral contraceptives are added to or withdrawn from a stable dosage regimen.

The desired effects of hypoglycaemic agents (including insulin), anti-hypertensives and diuretics are antagonised by corticosteroids.
The growth promoting effect of somatotropin may be inhibited by the concomittant use of corticosteroids.

Steroids may reduce the effects of anticholinesterases in myasthenia gravis and cholecystographic x-ray media.

The efficacy of coumarin anticoagulants and warfarin may be enhanced by concurrent corticosteroid therapy and close monitoring of the INR or prothrombin time is required to avoid spontaneous bleeding.

Concomitant use of aspirin and Non Steroidal Anti-Inflammatory Drugs (NSAIDs) with corticosteroids increases the risk of gastro-intestinal bleeding and ulceration.

The renal clearance of salicylates is increased by corticosteroids and steroid withdrawal may result in salicylate intoxication.

The hypokalaemic effects of acetazolamide, loop diuretics, thiazide diuretics, and carbenoxolone, are enhanced by corticosteroids. The risk of hypokalaemia is increased with theophylline and amphotericin. Corticosteroids should not be given concomitantly with amphotericin, unless required to control reactions.

The risk of hypokalaemia also increases if high doses of corticosteroids are given with high doses of bambuterol, fenoterol, formoterol, ritodrine, salbutamol, salmeterol and terbutaline. The toxicity of cardiac glycosides is increased if hypokalaemia occurs with corticosteroids.

Concomitant use with methotrexate may increase the risk of haematological toxicity.

High doses of corticosteroids impair the immune response and so live vaccines should be avoided (see also warnings).

4.6. Pregnancy and Lactation

The ability of corticosteroids to cross placenta varies between individual drugs, however, 88% of prednisolone is inactivated as it crosses the placenta.

Administration of corticosteroids to pregnant animals can cause abnormalities of foetal development including cleft palate, intra-uterine growth retardation and effects on brain growth and development. There is no evidence that corticosteroids result in an increased incidence of congenital abnormalities, such as cleft palate/lip in man. However, when administered for prolonged periods or repeatedly during pregnancy, corticosteroids may increase the risk of intra-uterine growth retardation.

Hypoadrenalism may, in theory, occur in the neonate following prenatal exposure to corticosteroids but usually resolves spontaneously following birth and is rarely clinically important. As with all drugs, corticosteroids should only be prescribed when the benefits to the mother and child outweigh the risks. When corticosteroids are essential however, patients with normal pregnancies may be treated as though they were in the non-gravid state.

Patients with pre-eclampsia or fluid retention require close monitoring. Depression of hormone levels has been described in pregnancy but the significance of this finding is not clear.

Lactation:

Corticosteroids are excreted in small amounts in breast milk. However doses of up to 40mg daily of prednisolone are unlikely to cause systemic effects in the infant. Infants of mothers taking higher doses than this may have a degree of adrenal suppression but the benefits of breast feeding are likely to outweigh any theoretical risk.

4.7. Effects on Ability to Drive and Use Machines

None known.

4.8 Undesirable Effects

The incidence of predictable undesirable effects, including hypothalamo-pituitary-adrenal (HPA) suppression, correlates with the relative potency of the drug, dosage, timing of administration and the duration of treatment (see Section 4.4).

The following side effects may be associated with the long-term systemic use of corticosteroids.

Infections and Infestations
Increased susceptibility and severity of infections with suppression of clinical symptoms and signs, opportunistic infections, recurrence of dormant tuberculosis (see section 4.4).

Neoplasms benign, malignant and unspecified (incl cysts and polyps)
Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy. Discontinuation of corticosteroids may result in clinical remission.

Blood and lymphatic system disorders
Leukocytosis.

Immune system disorders
Hypersensitivity including anaphylaxis has been reported.

Endocrine disorders
Suppression of the HPA axis.
Cushingoid.
Impaired carbohydrate intolerance with increased requirement for anti-diabetic therapy, manifestation of latent diabetes mellitus.

Metabolism and nutrition disorders
Sodium and water retention, hypokalaemia, hypokalaemic alkalosis, increased appetite, negative protein and calcium balance.

Psychiatric disorders
Euphoric mood, psychological dependence, depressed mood, insomnia, aggravation of schizophrenia.
A wide range of psychiatric reactions including affective disorders (such as irritable, euphoric, depressed and labile mood, and suicidal thoughts), psychotic reactions (including mania, delusions, hallucinations, and aggravation of schizophrenia), behavioural disturbances, irritability, anxiety, sleep disturbances, and cognitive dysfunction including confusion and amnesia have been reported. Reactions are common and may occur in both adults and children. In adults, the frequency of severe reactions has been estimated to be 5-6%. Psychological effects have been reported on withdrawal of corticosteroids; the frequency is unknown.

Nervous system disorders
Dizziness, headache.
Increased intracranial pressure with papilloedema in children (pseudotumour cerebri) -usually after treatment withdrawal.
Aggravation of epilepsy.

Eye disorders

Glaucoma, papilloedema, posterior subcapsular cataracts, central serous chorioretinopathy, exophthalmos, corneal or scleral thinning, exacerbation of ophthalmic viral or fungal diseases.

Ear and labyrinth disorders
Vertigo

Cardiac disorders
Myocardial rupture following recent myocardial infarction.
Congestive cardiac failure (in susceptible patients).

Vascular disorders
Hypertension, embolism.

Respiratory, thoracic and mediastinal disorders
Hiccups.

Gastrointestinal disorders
Dyspepsia, nausea, vomiting, abdominal distension, abdominal pain, diarrhoea, oesophageal ulceration, candidiasis, pancreatitis acute.
Peptic ulceration with perforation and haemorrhage.

Skin and subcutaneous tissue disorders
Skin Atrophy, skin striae, acne, telangiectasia, hyperhidrosis, rash, pruritus, urticaria, hirsutism.

Musculoskeletal and connective tissue disorders
Myopathy, osteoporosis, vertebral and long bone fractures, avascular osteonecrosis, myalgia.
Growth retardation in infancy, childhood and adolescence.

Reproductive system and breast disorders
Menstruation irregular, amenorrhoea.

General disorders and administration site conditions
Impaired healing, malaise.

Investigations
Weight increased.

Injury, poisoning and procedural complications
Tendon rupture, contusion (bruising).

Withdrawal Symptoms
Too rapid a reduction of corticosteroid dosage following prolonged treatment can lead to acute adrenal insufficiency, hypotension and death (See Section 4.4)

A ‘withdrawal syndrome’ may also occur including fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin nodules and loss of weight.

In some instances, withdrawal symptoms may involve or resemble a clinical relapse of the disease for which the patient has been undergoing treatment.

Other effects that may occur during withdrawal or change of corticosteroid therapy include benign intracranial hypertension with headache and vomiting and papilloedema caused by cerebral oedema.
Latent rhinitis or eczema may be unmasked.

4.9. Overdose

Treatment is unlikely to be needed in cases of acute overdosage.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

Prednesol/Soluble Prednisolone tablets contain the equivalent of 5mg of prednisolone in the form of the 21-disodium phosphate ester. Prednisolone sodium phosphate is a synthetic glucocorticoid with the same general properties as prednisolone itself and other compounds classified as corticosteroids. Prednisolone is four times as active as hydrocortisone on a weight for weight basis.

Prednisolone sodium phosphate is very soluble in water, and is therefore less likely to cause local gastric irritation than prednisolone alcohol, which is only slightly soluble. This is important when high dosages are required, as in immuno-suppressive therapy.

5.2. Pharmacokinetic Properties

Absorption
Prednisolone is readily absorbed from the gastrointestinal tract with peak plasma concentrations achieved by 1-2 hours after an oral dose. Plasma prednisolone is mainly protein bound (70-90%), with binding to albumin and corticosteroid-binding globulin. The plasma half-life of prednisolone, after a single dose, is between 2.5-3.5 hours.

Distribution
The volume of distribution and clearance of total and unbound prednisolone are concentration dependent, and this has been attributed to saturable protein binding over the therapeutic plasma concentration range.

Metabolism
Prednisolone is extensively metabolised, mainly in the liver, but the metabolic pathways are not clearly defined.

Excretion
Over 90% of the prednisolone dose is excreted in the urine, with 7-30% as free prednisolone, and the remainder being recovered as a variety of metabolites.

5.3. Pre-clinical Safety Data

No additional data of relevance.

5. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Sodium Acid Citrate	BP
Sodium Bicarbonate	Ph.Eur
Saccharin Sodium	BP
Povidone	BP
Erythrosine E127	HSE
Sodium Benzoate	Ph.Eur

6.2. Incompatibilities

None known.

6.3. Shelf-Life

2 years.

6.4. Special Precautions for Storage

Store below 25°C.
Protect from light.

6.5. Nature and Content of Container

The tablets are foil strip packed and supplied in cartons of 30 or 100 tablets.

6.6. Instructions for Use, Handling and Disposal

For detailed instructions for use refer to the Patient Information Leaflet in every pack.

7. MARKETING AUTHORISATION HOLDER

Waymade PLC trading as Sovereign Medical
Sovereign House
Miles Gray Road
Basildon
Essex
SS14 3FR

8. MARKETING AUTHORISATION NUMBER(S)

PL 06464/0914

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16 December 1999

10 DATE OF REVISION OF THE TEXT

14/06/2010

Appendix 2 - MHRA Manufacturer's Authorisation for Piramal Healthcare UK Limited

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY

On behalf of the Licensing Authority under:
The Human Medicines Regulations 2012 (SI 2012/1916)

Manufacturer's Authorisation - Investigational Medicinal Products

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SECTION 1A

1. Authorisation Number

MIA(IMP) Number: MIA(IMP) 29595

2. Name of Authorisation Holder

PIRAMAL HEALTHCARE UK LIMITED

3. Address(es) of manufacturing/importing site(s)
(All authorised sites should be listed if not covered by separate licences)

MHRA SITE NUMBER:	SITE NAME:	ADDRESS:
10933	PIRAMAL HEALTHCARE UK LIMITED	EARLS ROAD, GRANGEMOUTH, STIRLINGSHIRE, FK3 8XG, UNITED KINGDOM
18244	PIRAMAL HEALTHCARE UK LIMITED	WHALTON ROAD, MORPETH, NORTHUMBERLAND, NE61 3YA, UNITED KINGDOM

4. Legally registered address of Authorisation Holder

WHALTON ROAD, MORPETH, NORTHUMBERLAND, NE61 3YA, UNITED KINGDOM

5. Scope of authorisation and dosage forms

See Annex 2

6. Legal basis of authorisation

See Section 1B of authorisation.

7. Name of responsible officer of the competent authority of the member state granting the manufacturing authorisation

Sean Kaiser

8. **Date** 10/01/2013

SECTION 1A (continued)

9. Annexes attached

Annex 2

Optional Annexes

Annex 4 (Contract Laboratories)

Annex 5 (Name of Qualified Person)

Annex 6 (Name of Responsible Person)

Annex 8 (Manufactured/Imported products)

Annex 9 (Storage Sites)

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY

On behalf of the Licensing Authority under:
The Human Medicines Regulations 2012 (SI 2012/1916)

Manufacturer's Authorisation - Investigational Medicinal Products

SECTION 1B

1. This authorisation is granted in accordance with the provisions of the Medicines for Human Use (Clinical Trials) Regulations 2004 as amended [S.I. 2004/1031] which implement Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001.

2. It permits the authorisation holder named on page 1 of Section 1 of the authorisation to manufacture, assemble and/or import investigational medicinal products for human use in accordance with Regulation 41 of the Medicines for Human Use (Clinical Trials) Regulations 2004 as amended [S.I. 2004/1031] (as detailed in section 3 of this authorisation) and is subject to the provisions identified on page 2 of Section 1 of this authorisation.

3. In this document a Manufacturers Authorisation for Investigational Medicinal Products may be referred to as MIA(IMP) and the Medicines and Healthcare products Regulatory Agency (acting on behalf of the Licensing Authority as defined in Regulation 6 of The Human Medicines Regulations 2012 (SI 2012/1916) may be referred to as MHRA.

4. The authorisation holder must inform the MHRA, in advance, of any change to the details submitted by him and/or included in this authorisation. All changes must be approved by the MHRA to have effect. If the business should change hands, the company or person taking over the business will have to obtain a new authorisation before commencing the manufacture, assembly or importation of investigational medicinal products.

Attention is drawn to the structure of this authorisation (as detailed on page 4 of Section 1) and to its completeness in accordance with that structure. This is of particular relevance where the holder of the authorisation is using it as evidence to a third party in support of claims to carry out those operations and activities to which this authorisation applies on premises and using personnel covered by this authorisation.

SECTION 1B (continued)

5. Authorisation Structure

This authorisation is divided into three sections.

(a) Section 1 (this section) identifies the authorisation holder and the responsible officer for the issue of the authorisation. This section would not usually be replaced during routine variations of the authorisation unless the authorisation holder details are varied.

(b) Section 2 lists variations to the authorisation. A replacement section 2 will be issued each time the authorisation is varied.

(c) Section 3 contains the details relating to each site named on the authorisation. Where there is more than one site there will be more than one part to Section 3. When a variation is made to the details of a site named in Section 3 the relevant part of Section 3 will be replaced.

(d) The authorisation holder is required to attach to his authorisation any replacement pages issued by MHRA and to mark or destroy superseded pages as to render them invalid.

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6. Provisions

a) The provisions of Schedule 7 of the Medicines for Human Use (Clinical Trials) Regulations 2004 as amended [S.I. 2004/1031] shall apply to the authorisation. For manufacture and/or assembly Parts 1 and 2 of Schedule 7 apply and for importation Parts 1 and 3 of Schedule 7 apply in accordance with Regulation 40(4) of the Medicines for Human Use (Clinical Trials) Regulations 2004 as amended [S.I. 2004/1031] subject to Regulation 38(2).

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY

On behalf of the Licensing Authority under:
The Human Medicines Regulations 2012 (SI 2012/1916)

Manufacturer's Authorisation - Investigational Medicinal Products

SECTION 2

VARIATION HISTORY

This page will be amended if the licence is varied.

Date	Variation Detail
16/02/2005	Initial Application
16/08/2006	Variation
03/10/2006	Remove Mr. R. S. Duncan, Mr. S. Whyard and Mr. H. M. Wright as QP's. Add Mr. K. Reay as a QP, Replace Mr. C. M. Seller with Mr. A. Walker as the Person Responsible for Production. Replace Mr. S. Whyard with Mr. C. Rienewerf as the Person Responsible for QC.
22/06/2007	Variation to remove Mr McLellan and replace with Mr Allen, change name for site 18244, add Mr Miller as QP, replace QC with Mr Johnson, add sites: Butterworth Laboratories Limited, Wickham Laboratories Limited and Reading Scientific Services Limited.
25/10/2007	Variation to amend site types list & amend function list.
12/09/2008	Variation to add Ms L Ford as licence holder, communication, invoice and site contact. Also to amend site functions as requested at site 18244 and delete Mr K Reay as a QP from this site.
15/11/2008	Update licence to EUDRA GMP format.
19/12/2008	Variation to change name of company to Piramal Healthcare UK Limited and also make sure site 18244 reflects this name change. Also remove Mr S A Allen as a QP from site 18244.
29/01/2009	Variation to change legal registered address.
13/11/2009	Variation to add Mr J Johnson as an additional QP to Morpeth site, add Hormones and replace Mrs Lisa Ford with Mr Colin Rienewert as LHC/SC.
29/01/2010	Variation: Add Dr Caroline Mason as QP to Morpeth, Site 18244
05/01/2011	Variation to Mrs Clare Edwards as QP on Morpeth site., add Durham County Scientific Services as contract lab., add Stability Testing to site 38651 and and add section 2.2.4.3.
13/07/2012	Variation to add contract laboratories Gen-Probe, Intertek, NCIMB, Wickham Labs, . Add Grangemouth site, T delete site 2321038, replace A Walker with J Palmer, site 18244, add contract laboratory Almac Sciences remove wickham labs and replace with site 5994535. Remove site 2321038
07/09/2012	Variation to amend site activities, site 18244.
10/01/2013	Variation to site 18244: remove Jarrett Palmer and replace with Aidan Walker as PM and remove John Johnson and add Amanda Race as QC

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY

On behalf of the Licensing Authority under:
The Human Medicines Regulations 2012 (SI 2012/1916)

Manufacturer's Authorisation - Investigational Medicinal Products

SECTION 3

ANNEX 2 - SITE INFORMATION

SCOPE OF AUTHORISATION

Name and address of site:

SITE NAME:	PIRAMAL HEALTHCARE UK LIMITED
ADDRESS:	WHALTON ROAD, MORPETH, NORTHUMBERLAND, NE61 3YA, UNITED KINGDOM
MHRA SITE NUMBER:	18244

Type of products handled

Human Investigational Medicinal Products for phase I, II, III clinical trials (optional)

Authorised operations

Manufacturing Operations of Investigational Medicinal Products (according to Part 1)	Authorised
Importation of Investigational Medicinal Products (according to Part 2)	Authorised

ANNEX 2 – SITE INFORMATION (continued)

Part 1 – MANUFACTURING OPERATIONS OF INVESTIGATIONAL MEDICINAL PRODUCTS

- authorised manufacturing operations include total and partial manufacturing (including various processes of dividing up, packaging or presentation), batch release and certification, importation, storage and distribution of specified dosage forms unless informed to the contrary;
- quality control testing and/or release and batch certification activities without manufacturing operations should be specified under the relevant items;
- if the company is engaged in manufacture of products with special requirements e.g. radiopharmaceuticals or products containing penicillin, sulphonamides, cytotoxics, cephalosporins, substances with hormonal activity or other or potentially hazardous active ingredients this should be stated under the relevant product type and dosage form (applicable to all sections of Part 1 apart from sections 1.5.2 and 1.6)

1.1	**Sterile Investigational Medicinal Products**	**Manufacture**
1.1.1	**Aseptically Prepared (list of dosage forms)**	
	1.1.1.1 Large volume liquids	Not Authorised
	1.1.1.2 Lyophilisates	Not Authorised
	1.1.1.3 Semi-solids	Not Authorised
	1.1.1.4 Small volume liquids	Not Authorised
	1.1.1.5 Solids and implants	Not Authorised
	1.1.1.6 Other aseptically prepared products	Not Authorised

1.1.2	***Terminally Sterilised***	**Manufacture**
	1.1.2.1 Large volume liquids	Not Authorised
	1.1.2.2 Semi-solids	Not Authorised
	1.1.2.3 Small volume liquids	Not Authorised
	1.1.2.4 Solids and implants	Not Authorised
	1.1.2.5 Other terminally sterilised prepared products	Not Authorised
1.1.3	***Batch certification only***	Authorised

1.2	Non-sterile investigational medicinal products	Manufacture
1.2.1	***Non-sterile products (list of dosage forms)***	
	1.2.1.1 Capsules, hard shell	Authorised
	1.2.1.2 Capsules, soft shell	Not Authorised
	1.2.1.3 Chewing gums	Not Authorised
	1.2.1.4 Impregnated matrices	Not Authorised
	1.2.1.5 Liquids for external use	Not Authorised
	1.2.1.6 Liquids for internal use	Not Authorised
	1.2.1.7 Medicinal gases	Not Authorised
	1.2.1.8 Other solid dosage forms	Authorised
	1.2.1.9 Pressurised preparations	Not Authorised
	1.2.1.10 Radionuclide generators	Not Authorised
	1.2.1.11 Semi-solids	Not Authorised
	1.2.1.12 Suppositories	Not Authorised
	1.2.1.13 Tablets	Authorised

	1.2.1.14 Transdermal patches	Authorised
	1.2.1.15 Other non-sterile medicinal products Dry powder for oral use. Hormones.	Authorised
1.2.2	Batch certification only	Not Authorised

1.3	Biological investigational medicinal products	Manufacture
1.3.1	***Biological medicinal products (list of product types)***	
	1.3.1.1 Blood products	Not Authorised
	1.3.1.2 Immunological products	Not Authorised
	1.3.1.3 Cell therapy products	Not Authorised
	1.3.1.4 Gene therapy products	Not Authorised
	1.3.1.5 Biotechnology products	Not Authorised
	1.3.1.6 Human or animal extracted products	Not Authorised
	1.3.1.7 Other biological medicinal products	Not Authorised
1.3.2	***Batch certification only (list of product types)***	
	1.3.2.1 Blood products	Authorised
	1.3.2.2 Immunological products	Authorised
	1.3.2.3 Cell therapy products	Authorised
	1.3.2.4 Gene therapy products	Authorised
	1.3.2.5 Biotechnology products	Authorised
	1.3.2.6 Human or animal extracted products	Authorised
	1.3.2.7 Other biological medicinal products	Not Authorised

1.4	***Other investigational medicinal products or manufacturing activity*** (any other relevant manufacturing activity/product type that is not covered above e.g. sterilisation of active substances, manufacture of biological active starting materials (when required by national legislation), medicinal gases, herbal or homeopathic products, bulk or total manufacturing, etc).	**Manufacture**
1.4.1	**Manufacture of:**	
	1.4.1.1 Herbal products	Not Authorised
	1.4.1.2 Homoeopathic products	Not Authorised
	1.4.1.3 Biological active starting materials	Not Authorised
	1.4.1.4 Other	Not Authorised
1.4.2	**Sterilisation of active substances/excipients/finished products:**	
	1.4.2.1 Filtration	Not Authorised
	1.4.2.2 Dry heat	Not Authorised
	1.4.2.3 Moist heat	Not Authorised
	1.4.2.4 Chemical	Not Authorised
	1.4.2.5 Gamma irradiation	Not Authorised
	1.4.2.6 Electron beam	Not Authorised
1.4.3	**Others**	Not Authorised

1.5	*Packaging only*	Packaging
1.5.1	***Primary packing***	
	1.5.1.1 Capsules, hard shell	Not Authorised
	1.5.1.2 Capsules, soft shell	Authorised
	1.5.1.3 Chewing gums	Not Authorised
	1.5.1.4 Impregnated matrices	Not Authorised
	1.5.1.5 Liquids for external use	Not Authorised
	1.5.1.6 Liquids for internal use	Not Authorised
	1.5.1.7 Medicinal gases	Not Authorised
	1.5.1.8 Other solid dosage forms	Not Authorised
	1.5.1.9 Pressurised preparations	Not Authorised
	1.5.1.10 Radionuclide generators	Not Authorised
	1.5.1.11 Semi-solids	Not Authorised
	1.5.1.12 Suppositories	Not Authorised
	1.5.1.13 Tablets	Not Authorised
	1.5.1.14 Transdermal patches	Not Authorised
	1.5.1.15 Other non-sterile medicinal products	Not Authorised
1.5.2	**Secondary packing**	Authorised

1.6	**Quality control testing**	
	1.6.1 Microbiological: sterility	Not Authorised
	1.6.2 Microbiological: non-sterility	Authorised
	1.6.3 Chemical/Physical	Authorised
	1.6.4 Biological	Not Authorised

Any restrictions or clarifying remarks related to the scope of these Manufacturing operations:

ANNEX 2 – SITE INFORMATION (continued)

Part 2 – IMPORTATION OF INVESTIGATIONAL MEDICINAL PRODUCTS

- authorised importation activities without manufacturing activity
- authorised importation activities include storage and distribution unless informed to the contrary

2.1	**Quality control testing**	**Import**
	2.1.1 Microbiological: sterility	Not Authorised
	2.1.2 Microbiological: non-sterility	Authorised
	2.1.3 Chemical/Physical	Authorised
	2.1.4 Biological	Not Authorised
2.2	**Batch certification of imported medicinal products**	
2.2.1	***Sterile Products***	
	2.2.1.1 Aseptically prepared	Authorised
	2.2.1.2 Terminally sterilised	Authorised
2.2.2	***Non-sterile products***	Authorised
2.2.3	***Biological medicinal products***	
	2.2.3.1 Blood products	Authorised
	2.2.3.2 Immunological products	Authorised
	2.2.3.3 Cell therapy products	Authorised

	2.2.3.4 Gene therapy products	Authorised
	2.2.3.5 Biotechnology products	Authorised
	2.2.3.6 Human or animal extracted products	Authorised
	2.2.3.7 Other biological medicinal products	Not Authorised
2.2.4	***Other importation activities*** (any other relevant importation activity that is not covered above e.g. importation of radiopharmaceuticals, medicinal gases, herbal or homeopathic products, etc.)	
	2.2.4.1 Radiopharmaceuticals/Radionuclide generators	Not Authorised
	2.2.4.2 Medicinal gases	Not Authorised
	2.2.4.3 Herbal products	Not Authorised
	2.2.4.4 Homoeopathic products	Not Authorised
	2.2.4.5 Biological active starting materials	Not Authorised
	2.2.4.6 Other	Not Authorised

Any restrictions or clarifying remarks related to the scope of these importing operations:

ANNEX 5/6 – SITE INFORMATION (continued)

Personnel

Person Number	Name	Personnel Type			
		QP	TQP	PM	QC
128211	Mr A Walker	No	No	Yes	No
3065514	Mrs Clare Edwards	Yes	No	No	No
124955	Mr P Baines	Yes	No	No	No
1111646	Mr Colin Rienewerf	No	No	No	No
563178	Dr Caroline Mason	Yes	No	No	No
4184857	Mrs Amanda Race	Yes	No	No	Yes

Key to Roles:

QP – Qualified Person
TQP – Transitional Qualified Person
PM – Production Manager/Supervisor
QC – Person responsible for Quality Control

ANNEX 4 – CONTRACT LABORATORIES

MHRA SITE NUMBER:	LABORATORY NAME:	ADDRESS:
5712	Butterworth Laboratories Limited	54-56 WALDEGRAVE ROAD, TEDDINGTON, MIDDLESEX, TW11 8NY, UNITED KINGDOM
38651	READING SCIENTIFIC SERVICES LIMITED	READING SCIENCE CENTRE, WHITEKNIGHTS CAMPUS, PEPPER LANE, READING, BERKSHIRE, RG6 6LA, UNITED KINGDOM
41013	NCIMB Limited	FERGUSON BUILDING, CRAIBSTONE ESTATE, BUCKSBURN, ABERDEEN, AB21 9YA, UNITED KINGDOM
343945	INTERTEK ASG	PO BOX 42, HEXAGON TOWER, BLACKLEY, MANCHESTER, M9 8ZS, UNITED KINGDOM
383321	ALMAC SCIENCES LIMITED	ALMAC HOUSE, 20 SEAGOE INDUSTRIAL ESTATE, CRAIGAVON, COUNTY ARMAGH, BT63 5QD, UNITED KINGDOM
388368	GEN-PROBE LIFE SCIENCES	APPLETON PLACE, APPLETON PARKWAY, LIVINGSTON, WEST LOTHIAN, EH54 7EZ, UNITED KINGDOM
5994535	WICKHAM LABORATORIES LIMITED	HOEFORD POINT, BARWELL LANE, GOSPORT, HAMPSHIRE, PO13 0AU, UNITED KINGDOM

ANNEX 9 – STORAGE SITES

MHRA SITE NUMBER:	SITE NAME:	ADDRESS:
10933	PIRAMAL HEALTHCARE UK LIMITED	EARLS ROAD, GRANGEMOUTH, STIRLINGSHIRE, FK3 8XG, UNITED KINGDOM
18244	PIRAMAL HEALTHCARE UK LIMITED	WHALTON ROAD, MORPETH, NORTHUMBERLAND, NE61 3YA, UNITED KINGDOM