Preschool wheeze: **I**nflammation/Infection **G**uided **Ma**nagement (PrIGMa)

Use of pathological phenotype to determine optimal management for moderate to severe preschool wheeze

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Study Coordination Centre

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Sponsor

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Funder

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GLOSSARY OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
ASR	Annual Safety Report
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Authorisation
DMC	Data Monitoring Committee
GAfREC	Governance Arrangements for NHS Research Ethics
GCP	Good Clinical Practice
ICF	Informed Consent Form
Main REC	Main Research Ethics Committee
NHS R&D	National Health Service Research & Development
PI	Principal Investigator
PIS	Patient Information Sheet
QA	Quality Assurance
QC	Quality Control
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAR	Serious Adverse Reaction
SAE	Serious Adverse Event
SDV	Source Document Verification
SOP	Standard Operating Procedure
TMG	Trial Management Group

KEYWORDS

Inflammation, infection, preschool wheeze, phenotype, inhaled steroids, antibiotics, eosinophils, clinical guidelines

STUDY SUMMARY

TITLE: Use of pathological phenotype to determine optimal management for moderate to severe preschool wheeze

SHORT TITLE: Preschool wheeze: **I**nflammation/Infection **G**uided **Ma**nagement (PrIGMa)

RATIONALE: At least one-third of all children under 5 years suffer from wheezing and breathlessness, but despite the high incidence[1], there are few effective therapies[2]. Current guidelines recommend the management of preschool wheezing should be determined by clinical phenotype[3]. However, this is based predominantly on expert consensus with little evidence. The current guidelines have not been compared to other strategies. Current management does not take account of objective evidence of underlying inflammation or infection, however there is evidence to support that preschool wheezers have pathologically distinct phenotypes. This study will therefore determine the efficacy of treating preschool wheeze based on objective biomarkers of inflammation and presence of bacterial infection, and compare this to current clinical guidelines based management. This is a novel approach to managing preschool wheeze, which if effective, will have a significant impact on changing current clinical practice, and can be instituted within 5 years.

AIMS: To compare management of preschool wheeze using current clinical guidelines to management determined by eosinophilic inflammation in sputum or blood, and infection in sputum or oropharyngeal swabs
To determine numbers that would be needed to perform a large, multi-centre randomised trial comparing management according pathological phenotype to current clinical guidelines

DESIGN: Randomised, single blind, controlled trial comparing management of preschool wheeze based on inflammation and infection profile to current standard of care – the intervention will be over a 4 month period. This is a proof of concept study to determine feasibility of this approach and to obtain data to allow an assessment of numbers that would be needed for a larger randomised trial.

Subjects will be recruited from out-patient clinics and attend for a screening / research visit during which assessments of pathological phenotype (bacterial infection and inflammation) will be made from induced sputum and blood. Their clinical phenotype will be determined by the Consultant. Subsequently, patients will be randomised to one of two arms:

i) current clinical care (as directed by their Consultant)
ii) pathological phenotype based management – presence of eosinophilia in blood (≥~~3~~2%) or induced sputum (>2.4%) – will receive twice daily inhaled steroids (beclomethasone 200mcg bd) for 4 months, presence of bacterial infection in

induced sputum or oropharyngeal swab – will receive 4 weeks of antibiotics targeted to the isolate, IF BOTH eosinophilic inflammation AND infection are present, then inflammation alone will be treated for 4 months.

All patients will continue on as required bronchodilator therapy, and any other anti-inflammatory therapy (other than inhaled steroids) e.g. montelukast.

OUTCOME MEASURES:

Primary outcome – number of unscheduled healthcare visits (UHCV) during the 4 month intervention period

Secondary outcomes – health related quality of life, number of hospital admissions, number of days of oral steroids during the 4 month intervention period, and up to 1 year later

POPULATION: Preschool children, aged 1-5 years attending out-patient clinic for recurrent wheezing

ELIGIBILITY:

Age 1-5 years

≥ 2 courses of oral steroids (steroid bursts) OR hospital admissions in the last 12 months for acute wheezing, at least one of which is in the last 6 months

TREATMENT:

1. Inflammation / infection based management (pathological phenotype based management):

– use induced sputum and blood eosinophil count to determine whether regular inhaled steroids are prescribed for 4 months, or antibiotics are prescribed for 4 weeks (if sputum has a positive bacterial growth), if BOTH eosinophilic inflammation and bacterial infection are present, then treat the inflammation alone for 4 months

2. Current standard of care:

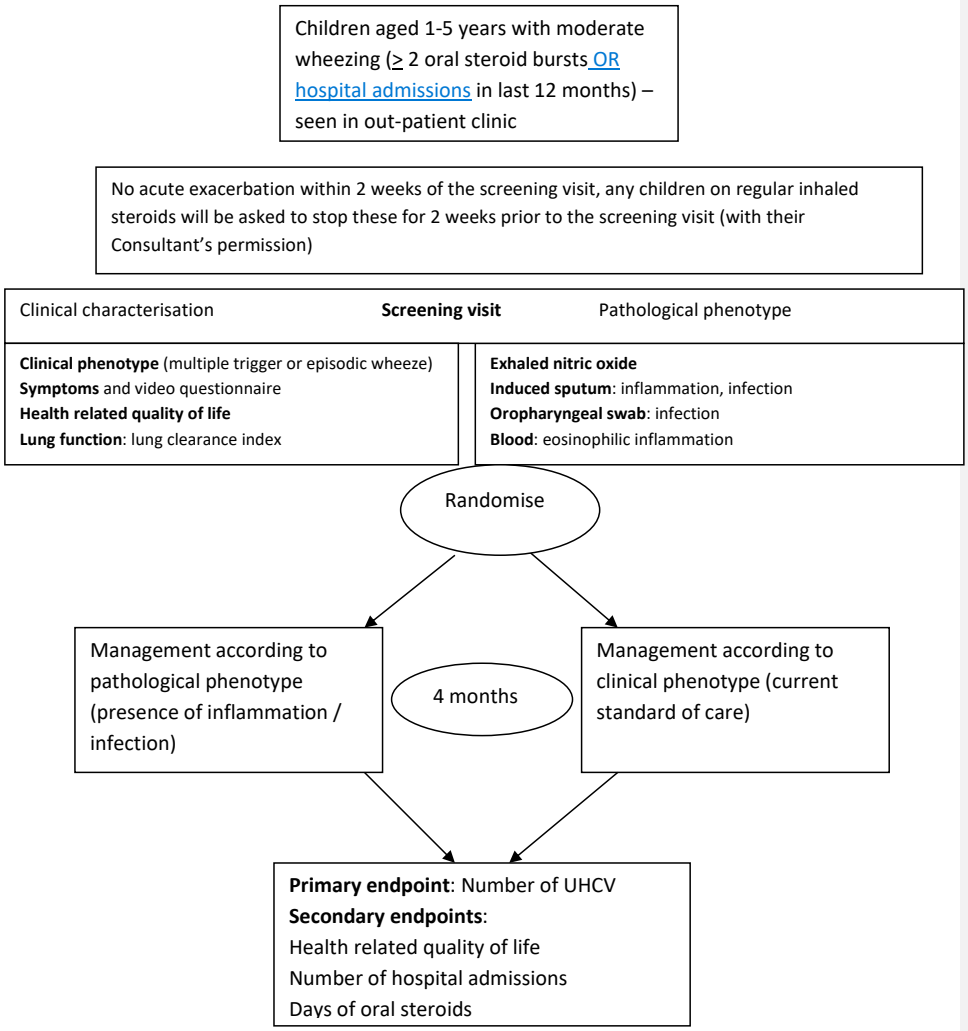
- Treat for 4 months as directed by the child's clinician – according to current clinical guidelines

DURATION:

Duration of intervention: 4 months

Duration of follow-up: after 4 months, then 6 monthly until the end of the trial.

REFERENCE DIAGRAM OF TRIAL DESIGN:



1. INTRODUCTION

1.1 BACKGROUND

At least one-third of all children under 5years suffer from wheezing and breathlessness, but despite the high incidence[1], there are few effective therapies[2]. Current guidelines recommend the management of preschool wheezing should be determined by clinical phenotype[3]. However, this is based predominantly on expert consensus with little evidence. The two clinical phenotypes are episodic wheeze, in which wheeze occurs during discrete episodes, usually in association with an upper respiratory tract infection, with no symptoms in between, and multiple trigger wheezing, with discrete episodes and symptoms in between[3]. The current approach has several limitations: i) It relies on accurate parental reporting of symptom pattern, which may not always be clearly distinguishable as episodic or multiple trigger. ii) Clinical phenotypes may switch within patients in a short period, such as only 3 months[4]. iii) The underlying infectious cause of acute episodes is not considered. Although it was previously thought that most episodes are precipitated by viral infections, it is now recognised that an equal number are also caused by bacterial infection[5]. The current guidelines have not been compared to other strategies. It is essential that the correct approach is adopted since therapeutic options include steroids[2], which if administered incorrectly result in adverse effects, the most worrying in the preschool age-group being reduced growth[6].

Evidence to support pathologically distinct preschool wheeze phenotypes

The pathology of allergic asthma in adults and school-aged children is characterised by airway eosinophilic inflammation and structural airway wall changes, termed airway remodelling[7]. Eosinophilia is usually steroid sensitive and thus the mainstay of therapy includes regular inhaled steroids. It is assumed that the preschool multiple trigger wheeze phenotype resembles allergic asthma and therefore is responsive to steroid therapy, whilst episodic wheeze is pathologically distinct and so is steroid unresponsive. Preschool wheezers have been shown to have bronchial eosinophilia[8;9]. Furthermore, we have shown that most episodic wheezers do not have eosinophilia, and pathologically resemble non-wheezing controls. Levels of exhaled nitric oxide (a non-invasive marker of airway inflammation) are more likely to be elevated in multiple trigger wheezers[10]. Lung function assessments also suggest multiple trigger wheezers have increased airway resistance and are distinct to episodic wheezers who have relatively normal lung function similar to controls[10]. Despite this evidence supporting pathophysiologically distinct phenotypes, preschool wheeze is still treated using clinical symptom patterns, without the additional use of inflammatory biomarkers to guide therapy. Importantly, data from adults with moderate asthma suggests use of inflammation guided therapy is superior in reducing exacerbations compared to clinical guidelines based therapy[11]. But, in children with severe asthma, the same approach was not

beneficial[12], suggesting the benefits of inflammation guided therapy may be influenced by disease severity.

The lower airway is not sterile and its microbial composition is altered in children with asthma[13], but this can only be detected using molecular biology techniques such as 16SPCR. Airway microbial composition in preschool children is unknown. However, it is established that a significant proportion of recurrent preschool wheezers have airway bacterial infection identified using traditional culture techniques[14]. An important unanswered question is the relevance of the microbial flora in determining recurrent wheezing in preschool children.

1.2 Rationale for Current study

Clinical Impact and Relevance

Wheezing and breathlessness in preschool children is common, but difficult to treat, and results in exacerbations requiring frequent healthcare visits. Of all UK admissions for children aged 1-16 years with acute wheeze or asthma between 1998-2005, approximately 75% of admissions each year were for children under 5 years old (median age 3 years), and the rate did not change over the seven year period[15]. In addition, caring for preschool children with wheeze cost the healthcare service an estimated £53 million in 1998/99, with the majority of costs being attributable to inpatient stays[16]. The costs to families caring for an unwell child at home or in hospital was between £10-40 per day, this was in addition to the costs of taking unforeseen time off work[16]. Current management of preschool wheeze is based on clinical phenotype alone and does not take account of objective evidence of underlying inflammation or infection. Given the drawbacks of parental recall bias, clinical phenotype switching and adverse effects of steroid therapy if used inappropriately, and the available evidence for pathologically distinct phenotypes in preschool wheezers, this study will determine the efficacy of treating preschool wheeze based on objective biomarkers of inflammation and presence of bacterial infection, and compare this to current clinical guidelines based management. This is a novel approach to managing preschool wheeze, which if effective, will have a significant impact on changing current clinical practice, and can be instituted within 5 years.

Since preschool wheezing is predominantly characterised by frequent exacerbations[2] and a sub-group of wheezers have evidence of eosinophilia (elevated exhaled nitric oxide, increased airway eosinophils), while others are likely to have evidence of airway bacterial infection[5;17;18], management based on objective evidence of inflammatory and infectious phenotype, rather than symptom pattern and clinical phenotype is an approach that warrants investigation. Importantly, the impact of disease severity and the optimal samples upon which to guide therapy also need investigation.

Hypothesis

Targeted treatment of preschool wheeze determined by airway inflammation and infection will result in better outcomes including fewer unscheduled healthcare visits, improved health related quality of life (HRQOL) for the child and family, and fewer days of oral steroid therapy compared to using current clinical guidelines.

2. STUDY OBJECTIVES

1. Compare treatment of recurrent wheezing in preschool children aged 1-5years with ≥2 courses of oral steroids for acute wheeze in the previous 12 months (at least 1 course in the previous 6 months) based on evidence of eosinophilic inflammation (blood or sputum eosinophils) and bacterial infection (oropharyngeal swabs) to current clinical guidelines.

2. Compare treatment efficacy of this approach in recurrent severe wheezers (those undergoing a clinically indicated bronchoscopy for severe symptoms) to moderate wheezers (those not undergoing bronchoscopy).

3. STUDY DESIGN

This is a single blind, randomised, controlled trial comparing management of moderate to severe preschool wheeze according to current clinical guidelines to management determined by inflammation and infection profile (pathological phenotype).

Study duration: The intervention phase of the study will last for 4 months, with follow-up immediately after the intervention period and 6 monthly thereafter until the end of the trial. The minimum follow-up is at the end of the 4 month intervention period, maximum follow-up will be for 3 years. During the 4 month intervention period, families will be contacted weekly by phone call for an update on unscheduled healthcare visits and symptoms.

Type of subjects to be recruited: All subjects will be aged between 1 and 5 years old. All subjects will have moderate to severe preschool wheeze, defined as ≥2 oral steroid bursts OR hospital admissions for acute wheeze in the last 12 months, with at least one oral steroid burst OR hospital admission in the last 6 months.

Number of subjects:

Based on published data for children with moderate preschool wheeze it is apparent that approximately five healthcare attendances occur per child per year[16]. In the current study, we wish to reduce the proportion of healthcare contacts by at least one-third per year. In order to achieve this with 80% power, and accepting statistical significance at the 5% level, we require a minimum of 36 evaluable patients with moderate wheeze per group. Evaluable patients are those from whom at least a blood sample to assess inflammation and an ororpharyngeal swab to determine infection can be obtained prior to randomisation.

A total of at least 72 children will therefore be recruited. However, this is the minimum number, and we aim to recruit 100 children (50 per group) if possible.

The number of subjects is not based on a precise power calculation as this is a proof of concept study to determine the feasibility of this approach, and to inform a future power calculation for a large multi-centre trial addressing the same question.

3.1 Study Outcome Measures: Primary outcome – number of unscheduled healthcare visits in the 4 month intervention period. Secondary outcomes – health related quality of life for the child and family, number of hospitalisations, days of oral steroids.

4. PARTICIPANT ENTRY

Patient recruitment at a site will only commence once the trial team has ensured that the following approval/essential documents are in place:

1. The main REC, and Clinical Trial Authorization (CTA) approval,
2. Final sponsorship and/or R&D approval (NHS Permission),
3. Sponsor has conducted the trial initiation procedure

Patient identification will take place at up to 5 sites (Royal Brompton Hospital, Kings College Hospital, Chelsea & Westminster Hospital, St Mary`s Hospital and Hillingdon Hospital, London ), all research visits, screening assessments, randomisation and drugs will be dispensed from the Brompton Hospital only. Kings College Hospital,Chelsea & Westminster Hospital, St Mary`s Hospital and Hillingdon Hospital will be used as patient identification (PIC) sites.

All sites participating in the trial will also be asked to provide a copy of the following:

1. Host site (R&D approval) and/or NHS Permission

All subjects who wish to enter the study will be fully screened and consented by the Chief Investigator, or one of the qualified clinicians involved in the study as Clinical Co-investigator.

4.1 Pre-randomisation Evaluations

All participants will undergo an initial research / screening visit which will involve the following tests:

Full blood count and Vitamin D

Total serum IgE and RASTs to house dust mite, grass pollen, tree pollen, cat, dog, aspergillus, milk, egg, peanut

Assessment of lung function by incentive spirometry and lung clearance index (LCI) using the multiple breath washout technique
Exhaled nitric oxide – using the offline tidal breathing technique
Sputum induction using nebulised hypertonic saline
Oro-pharyngeal swab
Symptom questionnaire
Health related quality of life questionnaire
Urine sample for cotinine levels (and for storage if parents consent)/salivary cotinine

4.2 Inclusion criteria

Age ≥ 1 years, < 6 years
Reported recurrent wheeze, needing at least 2 admissions +/- oral steroids in the last 12 months, at least one admission +/- oral steroids in the last 6 months

Past wheeze confirmed by a clinician

4.3 Exclusion criteria

Any known cardiac disease
Any chronic respiratory condition (other than preschool wheeze) diagnosed by a physician
Any chronic condition that increases susceptibility to respiratory tract infections such as severe developmental delay and feeding difficulty / unsafe swallow
Prematurity <34 weeks, or requirement of ventilation in the newborn period
History of neonatal chronic lung disease
Family not contactable by telephone

4.4 Withdrawal criteria

The trial will be analysed using an intention to treat approach.
The intervention arm or taking part in the trial will not affect the acute management of the child in any way, should the child become ill or develop symptoms, they should be taken to be seen by a healthcare professional in the usual way. Management of any acute episodes will not be influenced by the study or study team in any way. If during the 4 month intervention period the child's clinicians / healthcare workers suggest a change in the maintenance therapy is needed, then this will be undertaken without any negotiation. The study team will request that they are informed of the change, and the child will still be included in the analysis because of the intention to treat design.
If the participants wish to withdraw consent to take part in the study, the data obtained until the time of withdrawal will be used – as it is an intention to treat analysis – providing the participants agree. If however they do not wish for any of the data to be used or analysed, then all data will be destroyed. Parents / families will be free to withdraw at any stage, and that will not impact in any way on their child's routine clinical management.

5. RANDOMISATION AND ENROLMENT PROCEDURE

5.1 Randomisation practicalities

All randomisation and enrolment will occur during routine working hours – as all research visits will take place in the Biomedical Research Unit during the week between 9am and 5pm. Children will be recruited when they are clinically well, not during an acute attack.

We will use the Imperial INFORM database Unit to undertake randomisation

We wish to stratify randomisation according to sex and age, to achieve similar numbers of boys and girls in each group, and to have a similar average age for each group.

The age stratification will be as follows: >1- ≤3 years and >3 - ≤5 years

As wheezing in preschool children is a seasonal disorder (majority of symptoms and exacerbations occur between September – April each year), the baseline assessments and pre-randomisation visits will be arranged between late August – December each year, so that randomisation and intervention take place between September – January each year, to allow the 4 month intervention period to fall within the main season.

All patients will be given a study specific 24hrs emergency contact card immediately after being randomized. The card includes details of the study: Study title, patient trial number, CI/PI's contact details along with out of hours contact details in case of emergency.

5.2 Unblinding

The trial is a single blind trial. The parents of the children taking part and the physicians that decide the clinical management will be unaware of the arm the child has been randomised to, but the researcher will know – since the researcher will have to instruct the family on which treatment should be initiated once randomisation has occurred.

We do not foresee a need to unblind as there are no new treatments being trialled, we are using licenced treatments but with a novel indication. All doses to be used are also within licenced indications.

6. TREATMENTS

6.1 Treatment arms

The drugs to be used in the pathological phenotype arm include:

Beclometasone diproprionate metred dose inhaler with spacer – 100mcg per dose – 2 puffs twice a day
or
Antibiotics – augmentin duo (0.3ml/kg bd) or azithromycin (10mg/kg od) – therapeutic dose calculated according to the child's weight – for 4 weeks. The actual antibiotic used will be determined by the sensitivities of the organisms identified on bacterial culture. For children that are allergic to penicillin, azithromycin will be used instead of augmentin duo.

The drugs will be dispensed from the pharmacy at The Royal Brompton Hospital. If antibiotics are needed, a 4 week supply will be dispensed, and all children will be prescribed 4 weeks of therapy.
If the beclometasone inhaler is needed, sufficient doses for 4 months will be dispensed.

Management in the pathological phenotype arm:

1. **Eosinophilic inflammation, no bacterial infection:**

Children with sputum eosinophils >2.4% or blood eosinophils ≥3% will be defined as eosinophilic and management will be as follows:

i) Regular inhaled steroids (beclometasone 200 mcg bd) for 4 months in those previously not on any regular therapy.

ii) Of children who have already been prescribed inhaled steroid therapy, those with an eosinophilic phenotype will continue for a further 4 months.

iii) Children who have already been prescribed a regular leukotriene receptor antagonist will continue this and regular inhaled steroids (beclometasone 200mcg bd) will be added to their maintenance therapy for 4 months.

iv) Use of as required bronchodilator therapy will continue

2. Non-eosinophilic, no inflammation, no infection*:* Children with either sputum eosinophils ≤2.4% or blood esoinophils <3% will be defined as non-eosinophilic and management will be as follows:

i) Use of as required bronchodilators for acute symptoms

ii) Non-eosinophilic children that have already been prescribed regular inhaled steroids will be asked to stop them for 4 months

Children with no bacterial growth from oropharyngeal swab or induced sputum, and without eosinophilic inflammation will continue management according to the non-eosinophilic, no inflammation, no infection profile.

3. **Bacterial infection, no eosinophilic inflammation:** Children with a positive bacterial culture result from oropharyngeal swab or induced sputum will be treated with a 4 week course of antibiotics. Four weeks of antibiotic therapy will be used as this has been shown to be beneficial in a previous study of severe preschool wheeze[16]. If these children have already been prescribed regular inhaled steroids, they will be stopped for 4 months.

4. **Eosinophilic inflammation AND bacterial infection**: Children with raised eosinophils in induced sputum or blood AND positive bacterial culture will be managed according to the eosinophilic inflammation alone guideline. They will only be given inhaled steroids for 4 months, and no antibiotics. This is to assess only one intervention at a time. However, we do not anticipate many children will be in this group as our previous data shows those with positive bacterial cultures are very unlikely to have eosinophilia.

Management in the clinical guidelines arm:

The children will be treated as directed by their Consultant Paediatrician. The prescription for the drugs to be used will be dispensed from the pharmacy department at the Royal Brompton Hospital – as directed by the clinician. Usually only 2 weeks of medication is prescribed by the pharmacy, but for this trial 4 months' supply will be given.

6.2 Dose modifications for toxicity

All drugs to be used in the trial are already licenced for use in children of this age and in the doses to be used. Drug induced toxicity is therefore not a concern.

6.3 Premedication

There are no additional drugs that will be used before randomisation.

Concomitant treatment

The following medication will be allowed to continue during the intervention period in both study arms.

1. Use of rescue medication with bronchodilators for acute symptoms – salbutamol and/or ipratropium bromide
2. Use of leukotriene receptor anatagonist – montelukast – can continue regardless of whether it is being taken regularly or as required for acute symptoms

6.4 Interaction with other drugs

All drugs to be used are already licenced for use in children of this age. There are no other drugs that the child should not receive while they are in the trial and having the drug interventions for the trial.

6.5 Dispensing and Accountability

The following drugs will be sourced from routine hospital stock and their handling and management will be subject to standard procedures of the pharmacy.

Beclometasone diproprionate metred dose inhaler with spacer – 100mcg per dose
Augmentin duo syrup
Azithromycin syrup
The Pharmacy hospital department will be responsible for maintaining & updating the trial Accountability Log, filed in the hospital pharmacy file.

Route of administration, dosage, dosage regimen, and treatment period(s) of the medications

Beclometasone diproprionate – inhaled, 100 mcg – 2 puffs twice daily via mdi and spacer, for 4 months
Augmentin duo – oral, 0.3ml/kg twice daily for 4 weeks
Azithromycin – oral 10mg/kg once daily for 4 weeks

Assessment of compliance

All beclometasone inhalers will be fitted with an electronic monitoring device (Smartinhaler) in order to ensure the medication has been taken according to the regimen prescribed
The antibiotic for the full 4 week period will be dispensed from the hospital to help compliance
Parents will be phoned weekly to remind them of the importance of giving the child's treatment – whether that is the inhaler or antibiotics.

7. PHARMACOVIGILANCE

7.1 Definitions:

Adverse Reaction (AR): all untoward and unintended responses to a medication related to any dose administered. *All AEs judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a medicinal product qualify as adverse reactions.*

Unexpected Adverse Reaction: an AR, the nature or severity of which is not consistent with the applicable product information (eg investigator's brochure for an unapproved investigational product or summary of product characteristics (SmPC) for an authorised product*).*

Serious Adverse Event (SAE) or **Serious Adverse Reaction:** any untoward medical occurrence or effect that at any dose:

Results in death
Is life-threatening – *refers to an event in which the subject 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*
Requires hospitalisation, or prolongation of existing inpatients' hospitalisation
Results in persistent or significant disability or incapacity
I**s a congenital anomaly or birth defect**

An Unexpected Adverse Reaction is an Adverse Reaction, when both the nature and severity of the event is not consistent with the information about the medicinal product in question,

(a) in the case of a product with a marketing authorization, in the Summary of Product Characteristics (SmPC) for that product.

Terminology for classification of SAEs

1. Severity will be described using the following categories:

- **Mild**—the adverse event does not interfere with the volunteer's daily routine, and does not require intervention; it causes slight discomfort.
- **Moderate**—the adverse event interferes with some aspects of the volunteer's routine, or requires intervention, but is not damaging to health; it causes moderate discomfort.
- **Severe**—the adverse event results in alteration, discomfort or disability which is clearly damaging to health.

3. Expectedness will be described using following categories:

- **Expected**—an AE that is classed in nature as serious and which is consistent with the information about the drug listed in the SmPC**.**
- **Unexpected**—an AE that is classed in nature as serious and which is not consistent with the information about the drug listed in the SmPC.

Recording of Safety Information

Collection, recording and reporting of AEs (including serious and non-serious events and *reactions) to the Sponsor will be done according to the Sponsor's Pharmacovigilance SOP.*

Adverse Events (AEs)

All Adverse Events will be recorded in the hospital notes in the first instance.

A record of all AEs, whether related or unrelated to the treatment will also be kept in the CRF and the Sponsor's AE Log.

All drugs used in this trial are licensed in the UK and used within their marketing authorization.

The most up-to-date version of the SmPC will be used during the trial.

Contact details for reporting SAEs and SUSARs:
Fax: 0207 351 8763, attention Dr Sejal Saglani
Please send SAE forms to: Dr Sejal Saglani
Tel: 0207 352 8121 ext 8509

Annual Progress Reports (APRs)

The Chief Investigator will prepare the APR. It will be reviewed by the JRO and sent to the main REC within 30 days of the anniversary date on which the favourable opinion was given by the Ethics committee, and annually until the trial is declared ended.

Notification of Serious Breaches of GCP and/or the protocol

Any Protocol Deviations, Violations, Potential Serious Breaches and Urgent Safety Measures will be recorded using the Sponsor's Log issued during the Sponsor's Trial/Site Initiation meeting/visit.

Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations2004 [Statutory Instrument 2004/1031], as amended by Statutory Instrument2006/1928, contains a requirement for the notification of "serious breaches" of GCP or the trial protocol:

(1) The Sponsor of a clinical trial shall notify the licensing authority in writing of any serious breach of:

(a) The conditions and principles of GCP in connection with that trial; or

(b) the protocol relating to that trial, as amended from time to time in accordance with regulations 22 to 25, within 7 days of becoming aware of that breach.

(2) For the purposes of this regulation, a "serious breach" is a breach which is likely to effect to a significant degree:

(a) The safety or physical or mental integrity of the subjects of the trial; or

(b) The scientific value of the trial.

The Sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase. The Sponsor's SOP on the Protocol Violation/Deviations and Serious Breaches will be followed.

8. ASSESSMENT AND FOLLOW-UP

8.1 SCREENING ASSESSMENTS

All children aged between 1 and 5 years attending the out-patient clinic for reported recurrent wheeze will be eligible. No additional initial screening assessments will be made other than to ensure the child meets the inclusion and exclusion criteria outlined in Section 4.2 and 4.3 above.

8.2 BASELINE ASSESSMENTS

At the clinic appointment parents of eligible children will be approached and will be verbally informed about the study and given a written information sheet. Parents' contact details will be taken and after a few days will be telephoned to ask whether they would like to take part in the study. Once parents have agreed, they will be invited for a research visit for baseline assessments prior to randomisation.

As wheezing in preschool children is a seasonal disorder (main symptoms between September – April each year), the baseline assessments and pre-randomisation visits will be arranged between late August – December each year, so that randomisation and intervention take place between September – January each year, to allow the 4 month intervention period to fall in the main season.

All baseline assessments will be made providing the child has not had any acute wheezing episodes within the last 2 weeks. Also, with their Consultant's permission, parents will be asked to stop administering any regular inhaled steroids (if they have been taking them) for 2 weeks prior to the research visit.

The baseline assessments to be made at the research visit include:

Symptom questionnaire

Parents of all patients will complete a written questionnaire to obtain details of symptom duration, onset and severity, including history of medications, allergies, family history. All parents will also be shown a validated video questionnaire to obtain objective confirmation of wheeze(31). Health related quality of life (HRQOL) for the child and family will be determined using the validated Child Health Questionnaire(32-34).

Sample collection – all parents will be asked for consent for the child to undertake FeNO measurement, have a blood sample taken, undergo sputum induction and have an oropharyngeal swab taken.

1. Blood will be taken for a peripheral eosinophil count, total IgE and specific IgE to common aero and food allergens.

2. Sputum induction will be performed using nebulised hypertonic saline (3.5%), chest physiotherapy and oropharyngeal suction using previously described techniques for preschool children. We have now established a protocol for sputum induction in preschool children with various airways diseases, including wheezing, and have shown the procedure can be performed safely and with up to 95% success. Sputum will be processed for bacterial culture and cytology.

3. Lung function will be performed using the multiple breath washout technique to obtain a measurement of lung clearance index (LCI) as previously described, and according to recent American Thoracic Society recommendations. This technique does not require voluntary manoeuvres and needs minimal patient cooperation and is therefore suited to preschool children. We have recently performed a pilot feasibility study in preschool children attending the outpatient clinic, and demonstrated only 27% were able to perform LCI, but if the index was reduced to gas clearance in half the time (LCI0.5), the success rate increased to 77%. Importantly, it has been shown that LCI measurements can be reliably shortened in children to improve the feasibility of obtaining data. We will therefore perform LCI and LCI0.5 in this study, and will be able to use the data for more formal assessments of feasibility in preschool children with wheeze. This has not been reported to date. Incentive spirometry using computer aided incentive devices will also be performed, but the success of this is anticipated to be lower than that for LCI.

3. **Exhaled nitric oxide** will be measured using the offline tidal breathing technique, with samples assessed using the NiOX chemiluminescence analyser. The recently published reference values for preschool children will be used to define elevated values.
4. **5. Urine will be obtained and stored if parents consent to this.**

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8.3 TREATMENT PROCEDURE

The treatments to be used and each arm has been described in Section 6.1 above

8.4 SUBSEQUENT ASSESSMENTS

Children will not routinely be brought back for follow-up during the 4 month intervention period.

Their compliance with the treatment prescribed will be monitored using electronic monitoring devices for the inhaled treatment, and by weekly telephone calls by the research nurse to remind the family of the importance of making sure the treatment is given daily for the period prescribed.

A symptoms diary will not be kept by the parents during the intervention period, but an automated text will be sent to the parents daily asking whether or not their child had any

symptoms of wheeze in the last 24 hours – the answer to the text will be a simple "yes" or "no" response.

Immediate follow-up assessment:
After the 4 month intervention period, all children will be asked to return for a follow-up visit during which the following assessments will be made:
Symptoms – using symptom questionnaire
Health related quality of life questionnaire
Number of unscheduled healthcare visits in the 4 month period (these will also have been recorded during the weekly telephone calls)
Lung function assessment (using multiple breath wash-out technique as described in Section 8.2 above)
Exhaled nitric oxide measurement (using the offline tidal breathing technique as described in Section 8.2 above)
Sputum induction – to assess inflammation and infection
Urine- for storage if parents consent

Long-term follow-up assessments:
After the first follow-up visit at 4 months, parents of children will be contacted at 6 months by phone call to assess symptoms, unscheduled healthcare visits, courses of steroids and medication. They will also be asked to attend annually for a follow-up visit when all of the above plus lung function, exhaled nitric oxide and sputum induction will be performed. Urine samples will also be collected and stored if parents consent.These assessments will continue until the end of the trial period, or until the child reaches the age of 6 years, whichever is sooner.

8.5 LOSS TO FOLLOW-UP
All attempts will be made to stay in touch with families, initially weekly phonecalls will be undertaken during the intervention period to stay in touch, and subsequently, even if they do not wish to attend the hospital for follow-up visits, information will be obtained by phone call about symptoms, medication and unscheduled healthcare visits. If a family cannot be contacted, the GP and local hospital will be contacted to determine any change of address.

8.6 TRIAL CLOSURE
The minimum number of children to be recruited into each arm is 36, however, as this is a proof of concept study, an accurate power calculation cannot be performed, indeed part of the reason for this study is to determine the size of a larger trial that would be needed to definitively answer whether pathological phenotype based management is superior to current clinical guidelines. Therefore, recruitment of patients will continue until the end of the trial funding period, December 2018.

9.0 STATISTICS AND DATA ANALYSIS

Categorical data will be presented as number and percentage and comparisons between groups done using the chi squared or Fishers exact test. All numerical data will be tested for normality and normally distributed data will be presented as mean ± SD and comparisons between groups done using the 2 sample independent t test. For the data that are not normally distributed the median (IQR) will be presented and comparisons between groups done using the Mann-Whitney test. Poisson regression will be done to determine the factors the affect the primary endpoint, the number on unplanned hospital visits.

10.0 MONITORING

The trial will be monitored according to the monitoring plan agreed and written by the Sponsor, based on the internal risk assessment procedure. Where appropriate the CI will be asked to complete a copy of the Sponsor's self-monitoring template. It is the responsibility of the CI to ensure this is completed and submitted to the RO every on request (see Study Monitoring Plan). It is the responsibility of the RO to determine the monitoring risk assessment and explain the rationale.

Any urgent safety measures at either the CI or a PI site must be reported by that site Investigator within 3 days, as per UK Regulations.

11.0 REGULATORY ISSUES

11.1 ETHICS APPROVAL

The Study Coordination Centre has obtained approval from the London- Hampstead Research Ethics Committee. The Study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 19th World Medical Assembly, Helsinki 1964 and later revisions.

The Sponsor will ensure that the trial protocol, Patient Information Sheet (PIS), Informed Consent Form (ICF), GP letter and submitted supporting documents have been approved by the MHRA and a main Research Ethics Committee (REC), prior to any patient recruitment taking place. The protocol and all agreed substantial protocol amendments, will be documented and submitted for ethical and regulatory approval prior to implementation.

Before site(s) can enrol patients into the trial, the Principal Investigator must apply for Site Specific Assessment from the Trust Research & Development (R&D) and be granted written NHS R&D approval. It is the responsibility of the Principal Investigator at each site to ensure that all subsequent amendments gain the necessary approval. This does not affect the individual clinician's responsibility to take immediate action if thought necessary to protect the health and interest of individual patients (see section 12 for details of reporting procedures/requirements).

11.3 INFORMED CONSENT

Informed consent will be obtained by the Chief Investigator or a nominated deputy as recorded on Sponsor's Delegation of Responsibilities Log. All individuals taking informed consent will have received training in Good Clinical Practice (GCP).

Consent to enter this study will be obtained after a full account has been provided of its nature, purpose, risks, burdens and potential benefits, and the patient's parent/guardian has had the opportunity to deliberate. The patient will be allowed to specify the time they wish to spend deliberating, usually at least 24 hours, but up to several days.

The Investigator or designee will explain that the patients are under no obligation to enter the trial and that they can withdraw at any time during the trial, without having to give a reason and without prejudicing further treatment.

After the participant has entered the trial any clinician that is responsible for the participant (GP, local paediatrician or Consultant from the study centre) remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participant remains within the study for the purposes of follow-up and data analysis.

A copy of the signed Informed Consent Form (ICF) along with a copy of the most recent approved Patient Information Sheet (PIS) will be given to the participant's parent/guardian. The original signed consent form will be retained at the study site (one filed in the medical notes).

11.4 CONFIDENTIALITY

Participants' identification will be required for the registration process. The study coordination centre will preserve the confidentiality of participants taking part in the study. All data will be handled in accordance with the Data Protection Act 1998.

11.5 INDEMNITY

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study. NHS bodies are liable for clinical negligence and other negligent harm to individuals covered by their duty of care.

11.6 SPONSOR

Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS Trusts taking part in this study.

11.7 FUNDING

The trial has been funded by the NIHR as part of a Career Development Fellowship awarded to the CI (Dr Sejal Saglani).

11.8 AUIDITS AND INSPECTIONS

The study may be subject to inspection and audit by Imperial College London under their remit as Sponsor, the Study Coordination Centre and other regulatory bodies to ensure adherence to GCP.

12.0 TRIAL MANAGEMENT

A Trial Management Group (TMG) will be appointed and will be responsible for overseeing the progress of the trial. The day-to-day management of the trial will be coordinated through the Royal Brompton Hospital Study Coordination Centre. The TMG will be made up of the CI (Dr Saglani), the trial statistician, and Coordinator (Yvie Bingham/Laura Baynton).

13.0 PUBLICATION POLICY

All publications and presentations relating to the study will be authorised by the Trial Management Group. The first publication of the trial results will be in the name of the TMG, if this does not conflict with the journal's policy. If there are named authors, these will include at least the trial's Chief Investigator, Statistician and Trial Coordinator. Authorship of parallel studies initiated outside of the TMG will be according to the individuals involved in the project, but must acknowledge the contribution of the Trial Management Group in the Study Coordination Centre.

14.0 REFERENCES

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