PARENT-DETERMINED ORAL MONTELUKAST THERAPY FOR PRESCHOOL WHEEZE

(**W**heeze **A**nd **I**ntermittent **T**reatment**: WAIT)**

Study Protocol

Version 7

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Study Summary

Full Title	Parent-determined oral montelukast therapy for preschool wheeze with stratification for Arachidonate-5-Lipoxygenase (ALOX5) promoter genotype
Short Title	Wheeze and Intermittent Treatment (WAIT)
Protocol Version Number and Date	Version 7 dated 24th June 2011
Methodology	Randomised, double-blind, placebo-controlled trial
Study Duration	3 years
Study Centres	Barts and The London NHS Trust; University of Leicester NHS Trust, Grampian NHS Trust (others may be added as required – see appendix)
Primary objective (phase of trial)	To determine whether parent-initiated intermittent treatment with oral montelukast in preschool children reduces the need for unscheduled medical attention for upper or lower respiratory tract infection or wheeze (Phase 3 trial).
Number of Subjects/Patients	1300
Main Inclusion Criteria	• Medical record diagnosis of wheeze, two previous attacks of wheeze one being within the last 3 months. • Age ≥ 10 months and ≤ 5.0 years at recruitment
Statistical Methodology and Analysis	The incident rate ratio (relative risk) and 95% confidence interval for need to seek unscheduled medical attention.

Glossary of Terms and Abbreviations

AE	Adverse Event
ACT	Asthma Control Test
AR	Adverse Reaction
ALOX5	membrane bound 5-lipoxygenase
ASR	Annual Safety Report
CA	Competent Authority
Child	An individual who takes part in this clinical trial
CI	Chief Investigator
cLT	Cysteinyl Leukotriene
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
DMC	Data Monitoring Committee
EC	European Commission
EMEA	European Medicines Agency
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
GAfREC	Governance Arrangements for NHS Research Ethics
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator Brochure
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISRCTN	International Standard Randomised
IVDMIA	*In vitro* diagnostic multivariate index assay
JRO	Joint Research and Development Office
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency

MS	Member State
Main REC	Main Research Ethics Committee
NHS R&D	National Health Service Research & Development
PAG	Parental Advisory Group
PI	Principle Investigator
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person for release of trial drug
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAR	Serious Adverse Reaction
SAE	Serious Adverse Event
SDV	Source Document Verification
SOP	Standard Operating Procedures
SmPC	Summary of Product Characteristics
SSA	Site Specific Assessment
SSAR	Suspected Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
URTI	Upper Respiratory Tract Infection

1. Introduction

1.1 Background

A quarter of preschool children between 1 and 5 yrs of age will develop at least one attack of wheeze[1]. The majority of affected children have several attacks of wheeze triggered by viral-colds, with minimal or no symptoms between attacks[2]. A minority of preschool children will also wheeze between colds. Preschool wheeze is a major clinical problem, with significant costs to primary and secondary care[3-4]. There are at least 2 clinical patterns of preschool wheeze; episodic viral-triggered wheeze which affects the majority of wheezing children, and multiple trigger wheeze which affects the minority. A promising therapy for both clinical phenotypes of wheeze is montelukast (trade name; Singulair), currently the only cysteinyl leukotriene (cLT) receptor antagonist licensed for young children. This beneficial effect of inhibition of cLT, a class of potent bronchoconstrictors, in preschool wheeze was suggested by our study of urinary cysteinyl leukotrienes, where levels of urinary LTC_4 were elevated during acute attacks of preschool wheeze, then fell into the normal range on convalescence [5]. A study relevant to "multi-trigger" preschool wheeze is a RCT of 689 young children where regular oral montelukast given over a 12 month period reduced the rate of exacerbations by 30%[6]. For episodic (viral) preschool wheeze Bisgaard *et al*[7] reported that regular daily use of oral montelukast over 12 months reduced the rate of preschool wheezing episodes by 32% compared with placebo. We recruited a heterogeneous group of children aged between 2 and 14 years with intermittent asthma into a 12-month placebo-controlled randomised controlled trial of oral montelukast (Pre-Empt study). Trial medication was started at the onset of a viral upper respiratory tract infection and continued for a minimum of 7 days, or until symptoms had resolved for 48 hours[8]. The montelukast-treated group had 162 unscheduled health-care resource utilisations for wheeze compared to 288 in the placebo group, and symptoms were significantly reduced by 14% in the montelukast treated group[8]. Since intermittent therapy may be effective in preschool wheeze, the aim of this trial is to assess whether parent-initiated montelukast therapy is efficacious in this condition.

The beneficial effect of montelukast, albeit consistent, is clinically relatively "modest" [8]. The overall modest benefit of montelukast is thought due to marked heterogeneity of response; i.e. some children respond very well while others do not respond at all. One explanation for this marked heterogeneity in response is variations in genes coding for components of the LT pathway[9]. The first step in LT production is the conversion of LTA_4 by membrane bound 5-lipoxygenase (ALOX5; other names for ALOX5 being 5-LO, and leukotriene A4 synthase) and 5-LO-activating protein (FLAP; encoded by the ALOX5P gene). The regulatory domain of ALOX5 controls leukotriene synthesis by catalysing the conversion of arachidonic acid to 5(S)-HETE, and further dehydration to the leukotriene A_4. The ALOX5 promoter polymorphism results in a variation in the number of SP1 transcription factor-binding motifs – which alters transcription factor binding, and influences 5-LOX gene expression[10]. Five SP1 repeats in the ALOX5 promoter are classified as the "wild" type, with other numbers of repeats reflecting the "mutant" genotype. Lima *et al* [11] found that adults carrying a variant number of repeats on one allele [x/x or 5/x] (where x is not equal to 5) have a 73% reduction in the risk of having an asthma attack on montelukast compared with homozygotes for the 5-repeat (5/5; wild-type) allele. We therefore hypothesise that overall, parent-initiated

montelukast therapy in preschool wheeze will be clinically moderately effective, but that there will be a highly-responsive subgroup of children defined by ALOX5 polymorphism status (i.e. carrying a variant number of repeats on one allele). In this trial we therefore include a stratification step for ALOX5 promoter polymorphism status, to ensure that an equal number of children with the variant and wild type number of SP1 repeats in the ALOX5 promoter receive placebo and active medication.

1.2 Investigational Medicinal Product (IMP)

IMP1 is Montelukast Granules (Merck Sharp and Dohme Limited). It comes as white granules 4 mg per sachet with Mannitol excipient. It is licensed in the UK for use as add-on therapy in children aged 6 months to 5 years with "mild to moderate persistent asthma" who are "inadequately controlled on inhaled corticosteroids" (MA number PL 0025/0440). It will be administered by parents over a period of one year. Since we found that overprinting the label is an unsatisfactory method of blinding, the IMP1 will be repackaged using identical packaging material to the licensed medication, but with no manufacturer identification label. Repackaging will be done by Nova Labs (Leicester). Since we are only repackaging, a simplified IMPD dossier will be submitted with the CTA application for the IMP.

The **IMP PL1 placebo** is the excipient Mannitol EP (Pearlitol SD 200). Granules will have identical morphology and taste to IMP1. It is thus identical in every respect except for the absence of montelukast. The placebo will be prepared in identical packaging to the active drug by Nova Labs (Leicester).

1.3 Preclinical Data

The cysteinyl leukotrienes are potent inflammatory eicosanoids released from various cells including mast cells and eosinophils. These important pro-wheezing mediators bind to cysteinyl leukotriene receptors (CysLT) found in the human airway and cause airway actions, including bronchoconstriction, mucus secretion, increased vascular permeability, and eosinophil recruitment. Montelukast is an orally active compound which binds with high affinity and selectivity to the $CysLT_1$ receptor, and is the only compound in the class which is licensed for use in young children[12].

1.4 Clinical Data

1.4.1 Laboratory studies

In clinical studies, montelukast inhibits bronchoconstriction due to inhaled leukotriene at doses as low as 5 mg (reviewed in SMPC document[12]).

1.4.2 Intervention studies

In a 12-month, placebo-controlled study in paediatric patients 2 to 5 years of age, montelukast 4 mg once daily improved parameters of asthma control compared with placebo irrespective of concomitant controller therapy (inhaled/nebulised corticosteroids or inhaled/nebulised sodium cromoglycate). Sixty percent of patients were not on any other controller therapy. Montelukast improved daytime symptoms (including coughing, wheezing, trouble breathing and activity limitation) and night-time symptoms compared with placebo. Montelukast also decreased "as-needed" β-agonist use and corticosteroid rescue for worsening asthma compared with placebo. Patients receiving montelukast had more days without asthma than those receiving placebo. A treatment effect was achieved after the first dose. In a 12-month, placebo-controlled study in paediatric patients 2 to 5 years of age with mild asthma and episodic exacerbations, montelukast 4 mg once daily significantly ($p \leq 0.001$) reduced the yearly rate of asthma exacerbation episodes (EE) compared with placebo (1.60 EE *vs*. 2.34 EE, respectively), [EE defined as ≥ 3 consecutive days with daytime symptoms requiring β_2-agonist use, or corticosteroids (oral or inhaled), or hospitalisation for asthma]. The percentage reduction in yearly EE rate was 31.9%, with a 95% CI of 16.9, 44.1. [7]

1.5 Rationale and Risk/Benefit Assessment

1.5.1 Risks.

Montelukast is licensed for use in preschool children (6 months to 5 years) as a continuous "add on" therapy[12]. No child will be denied the main therapy for wheeze in this age group i.e. "as required" inhaled short acting beta-2 agonist (salbutamol). Side effects of montelukast are mild, with a slight excess of headache, ear infection, sore throat, and upper respiratory infection reported in paediatric studies. These side effects have been reported with continuous use and are probably less likely to occur with intermittent therapy. Montelukast can be safely given with all other anti-asthma medications. All children will receive "as required" inhaled salbutamol, and if clinically indicated, may receive regular inhaled corticosteroids. A child may be withdrawn from the trial if they experience a serious adverse event which necessitates withdrawal, or if continuous oral montelukast is prescribed.

1.5.2 Benefits

A recent audit of "asthma" admission in children covering 67 hospitals during the period 1998-2005, found that 75% of 9,429 admissions were for preschool wheeze[3]. Since this was a secondary care-based audit, it very likely underestimates the total number of unscheduled attendances for preschool wheeze. A therapy that reduces the number of severe attacks will therefore have a major benefit to the NHS and children.

2 Study Aims and Objectives

The principal objective of this research is to determine whether intermittent treatment with oral montelukast in preschool children reduces the need for unscheduled medical attention for wheeze. Treatment (IMP) will be initiated by parents or guardians at the onset of every viral upper respiratory tract infection or wheezing episode and continued for 10 days.

3 Investigational plan

3.1 Overall Design

Randomised, double-blind, placebo-controlled clinical trial

Schema (Key: V = Visit, T = Telephone call, wk = week, m = month, *= in a subgroup of parents)

	V1		V2	T1	T2	T3	T4	T5	T6	V3*
	-2 wk	-1 wk	0 wk	+2m	+4m	+6m	+8m	+10m	+12m	+12m
Informed consent	X									
Check eligibility criteria	X									
Record baseline clinical and demographic data	X									
Review concomitant medications and need for medical attention	X		X	X	X	X	X	X	X	X
Collect saliva sample for DNA	X									
Qualitative assessment of parental views*			X							X
Height, weight of child	X									
Collect urine sample for urinary leukotriene	X									
Collect urine sample for urinary leukotriene during exacerbation*			X In the subset of children attending ED during an exacerbation – timing therefore unspecified x							
Train parents on use of IMP and use of inhaled short-acting beta-2 agonist			X							
Establish *ALOX5* polymorphism status		X								
Randomisation		X								
Withdraw IMP from pharmacy for initial issue/reissue			X	X – timing variable, depends on expiry date or date initial supply exhausted						
Supply IMP to parents			X							
Adverse event recording			X	X	X	X	X	X	X	X

3.3 Overview of Study Population

The study population will comprise preschool children (10 months to 5 years inclusive) with two previous episodes of wheeze.

3.4 Target Accrual

Target accrual is 1300 children.

4 Subject Selection

4.1 Inclusion Criteria

- age ≥ 10 months and ≤ 5 years on the day of the first dose of IMP.
- two or more attacks of parent-reported wheeze.
- at least one attack with wheeze validated by a clinician (nursing or medical)
- the most recent attack within the last 3 months.
- contactable by telephone and able to attend one face-to-face review
- parent or guardian able to give written informed consent for their child to participate in the study.

4.2 Exclusion Criteria

- any other chronic respiratory condition diagnosed by a clinician including structural airway abnormality (e.g. floppy larynx) and cystic fibrosis
- any chronic condition that increases vulnerability to respiratory tract infection such as severe developmental delay with feeding difficulty or sickle cell disease
- history of neonatal chronic lung disease
- current continuous oral montelukast therapy
- in a trial using an IMP in the previous 3 months prior to recruitment.

5 Study Procedures and Schedule of assessments

5.1 Informed consent procedures

5.1.1 Gaining Consent

The investigator, or a suitably trained person delegated by the investigator (who may be a research nurse or a research assistant who has attended a UK regulations GCP training course) will give an adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study. They will then obtain written informed consent from the parent or guardian prior to participation in this study.

5.1.2 Consideration Time

At least 24 hr or one overnight stay will be allowed for consideration by the parent or guardian before they consent to enter the study.

5.1.3 Freedom to Withdraw

During the consent process, the investigator, or person delegated by the investigator, will explain that parents or guardians are completely free to refuse to enter the study or to withdraw at any time during the study, for any reason.

5.1.4 New Information

If new safety information results in significant changes in the risk/benefit assessment for this trial, the consent form will be reviewed and updated if necessary. All children, including those already being treated, will be informed of the new information, provided with a copy of the updated consent form, and asked to give their consent to continue in the study.

5.2 Screening and Registration procedures

5.2.1 Invitation of potential study participants to attend screening visit

A member of the child's usual GP care team or the hospital paediatric team (as appropriate) will identify potentially eligible children based on age and history of wheeze from reviewing surgery and emergency department records. He/she will then approach the child's parents or guardian in person or by posting an invitation letter and or information sheet, to ask if they would like to be contacted about the study by a member of the research team. Individuals who agree to be contacted about the study will then be contacted by a research nurse or research assistant, who will briefly describe the study to them, and ask them if they would like to read a parent information sheet (PIS) if not already given. The research nurse or research assistant will then post or give a PIS to parents who express an interest in the study; those who subsequently confirm their interest in participation will be re-contacted and offered a screening appointment at a study site. A second invitation letter will be posted to individuals who do not respond to the first invitation letter.

5.2.2 Preparation for screening visit

Potential participating parents will be offered a screening appointment. They will also be asked to bring their child's usual asthma medication with them when they attend the screening visit.

5.2.3 Screening visit #1 (-2 weeks)

At the screening visit, an investigator, research nurse or research assistant will obtain written informed consent for participation in the trial from parents who are willing to take part in the study. The eligibility of children to participate in the study will then be assessed according to the criteria documented in sections 4.1. and 4.2. The parents of all eligible children will be asked to complete baseline assessments of their child's wheeze status including recording of baseline demographic and clinical data and details of concomitant medications, measurement of weight and height, taking a salivary sample using the Oragene paediatric collection system for extraction of DNA and assessment of leukotriene-associated genes, and obtaining a urine sample for leukotriene analysis. A follow-up appointment will be arranged for the issue of the IMP.

5.2.4 (-1 week)

DNA will be extracted from the salivary sample in the Institute for Cell and Molecular Science, Barts and the London, and children assigned to either ALOX5 promoter polymorphism "5/5", or "[5/x and x/x]" genotype. Extracted DNA will be stored at -70^{O}C for batch analysis of >50 polymorphisms in 10 genes encoding components of the LT biosynthetic pathway and the LT receptors. The local pharmacist will then assign a randomisation number to that child as per section 5.5 of this protocol, and withdraw the corresponding IMP from pharmacy on behalf of that subject.

5.2.5 Visit #2 (0 months)

The research nurse or research assistant will meet with parents, concomitant medications will be reviewed, and if all baseline data has been collected satisfactorily, issue parents the box containing 50 sachets of the IMP. Children whose parents are willing to participate but who do not meet eligibility criteria (i.e. no wheeze attack within 3 months) at their initial screening visit may be reassessed if they subsequently meet the eligibility criteria at some time in the future. Parents will be taught how to use the IMP, as well as inhaled "as required" salbutamol metered dose inhaler and spacer.

In a subgroup of 30 families, we will conduct qualitative interviews to establish attitudes towards genetic testing to develop personalised therapy, acceptability of parent-initiated therapy for preschool wheeze, the expected advantages and disadvantages of using the IMP, and their views on consent process and parent information sheet. In these families a further qualitative interview will be done at a visit date convenient to the family (visit 3 - see 4.7) to establish their attitudes towards genetic testing to individualise therapy, acceptability of parent-initiated therapy for preschool wheeze, their experience of using the trial medication, and the difficulties and advantages with parent-initiated therapy. Either one parent will be interviewed or, if they prefer, a joint interview with both parents will be done. Where possible, interviews will be done at the parental home. Interviewing, transcribing, and analysis of interviews will be done by a research assistant.

5.3 Randomisation procedures

Nova Laboratories Ltd (Leicester) will prepare a minimum of 2600 boxes of IMP for this trial. Preparation will be done in batches every 6 months (depending on recruitment rate). 1300 boxes will contain 50 sachets each containing montelukast (**IMP1**) and 1300 boxes will contain 50 sachets of placebo. Boxes will be allocated randomisation numbers in blocks of ten using a computer-generated random sequence. Nova Laboratories Ltd will be responsible for generation of the random number sequence and labelling boxes accordingly. Boxes bearing randomisation numbers will be delivered to the pharmacy at participating sites. Nova Laboratories will produce additional boxes of IMP for those children whose medications are lost, expire, or are exhausted such that they require more than two boxes during the one year follow-up period.

5.4 Treatment procedures

IMP will be presented as white granules administered either directly in the child's mouth, or mixed with a spoonful of cold or room temperature soft food (e.g., applesauce, ice cream, carrots and rice). The white sachet containing the granules should not be opened until ready to use. After opening the sachet, the full dose of granules must be administered within 15 minutes. If mixed with food, the granules must not be stored for future use. The granules are not intended to be dissolved in liquid for administration. However, liquids may be taken by the child subsequent to administration. The granules can be administered without regard to the timing of food ingestion. The dose is 1 sachet per day, started when the child has evidence of a viral cold or has wheeze, and stopped after 10 days. If a child vomits after the administration of the IMP no additional dose is given, and parents record this on the diary chart.

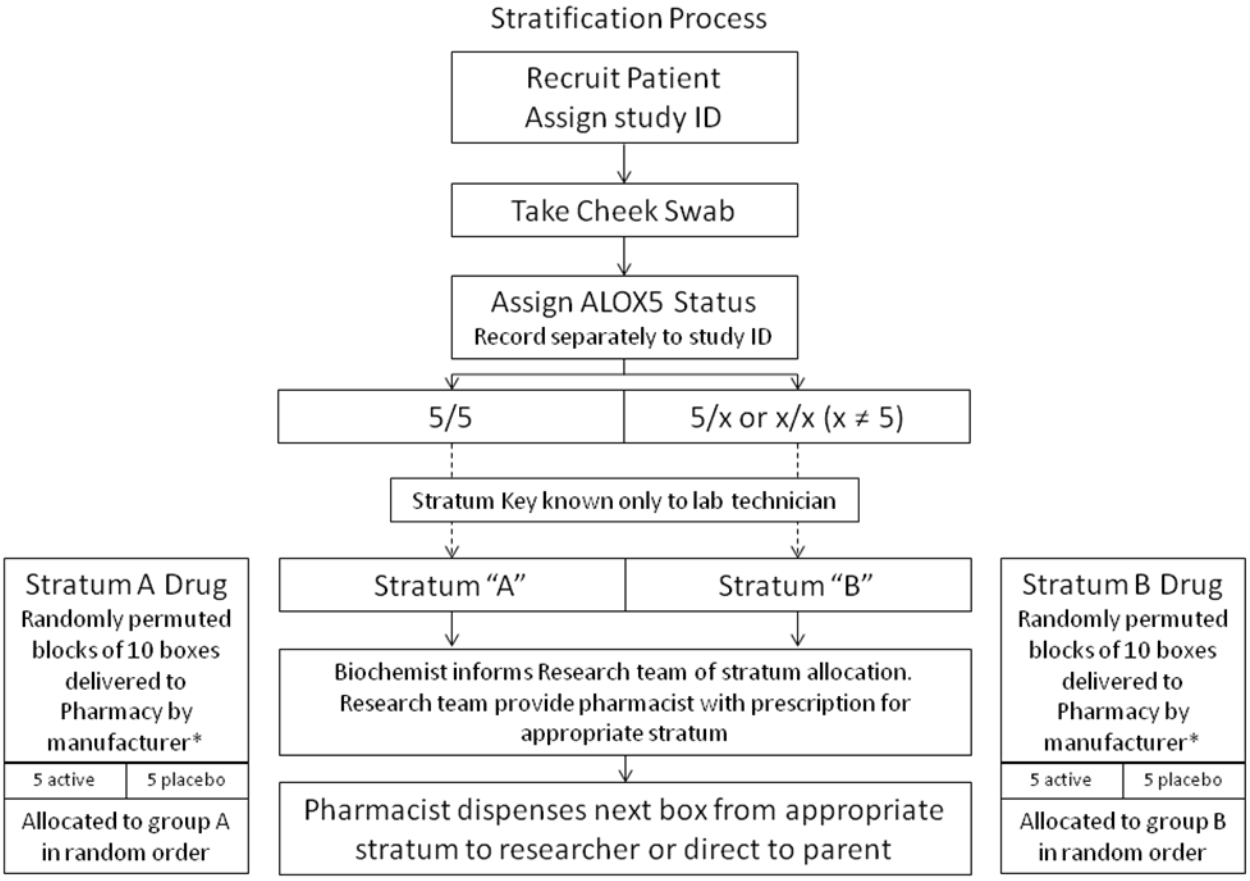
5.5 Method for assigning subjects to treatment group

Randomisation will be stratified according to ALOX5 promoter polymorphism status. This will yield two genotype groups:

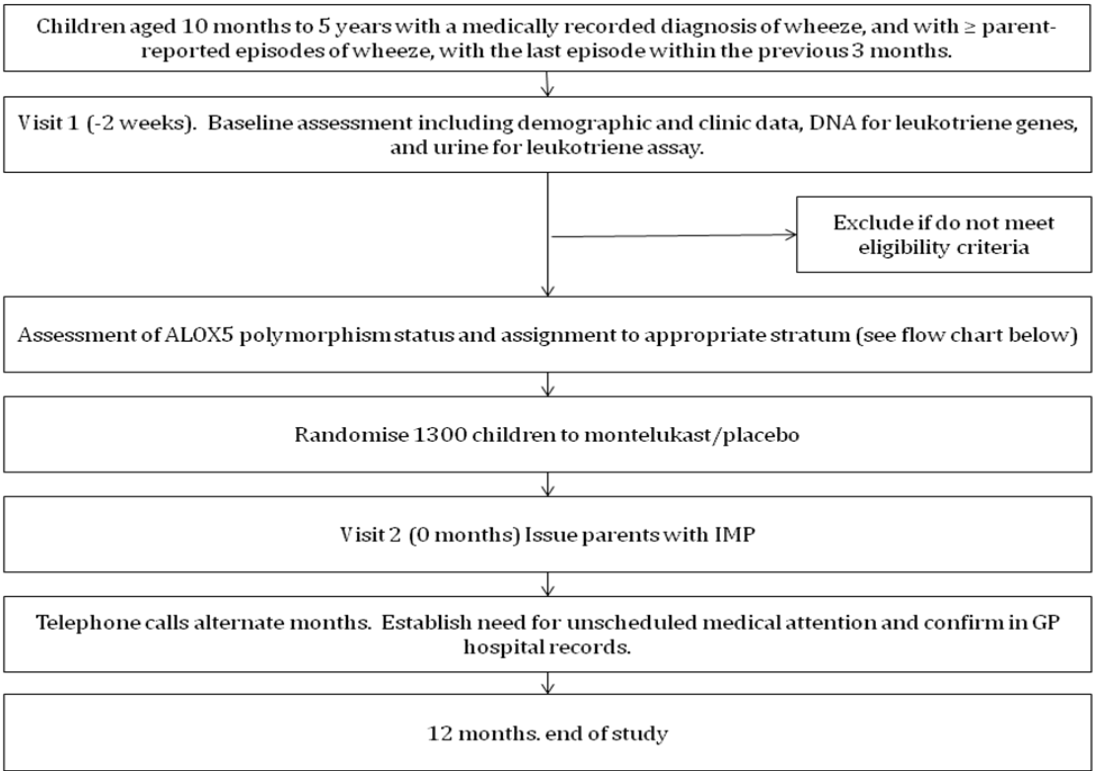
> **Group I** Children with the [5/5] ALOX5 promoter polymorphism genotype.
> **Group II** Children with [5/x and x/x]" ALOX5 promoter polymorphism genotype; where x is > or < than 5 SP1 repeats. (Groups will be referred to as Stratum A or B – all trial staff will be blinded to this relationship except the laboratory technician).

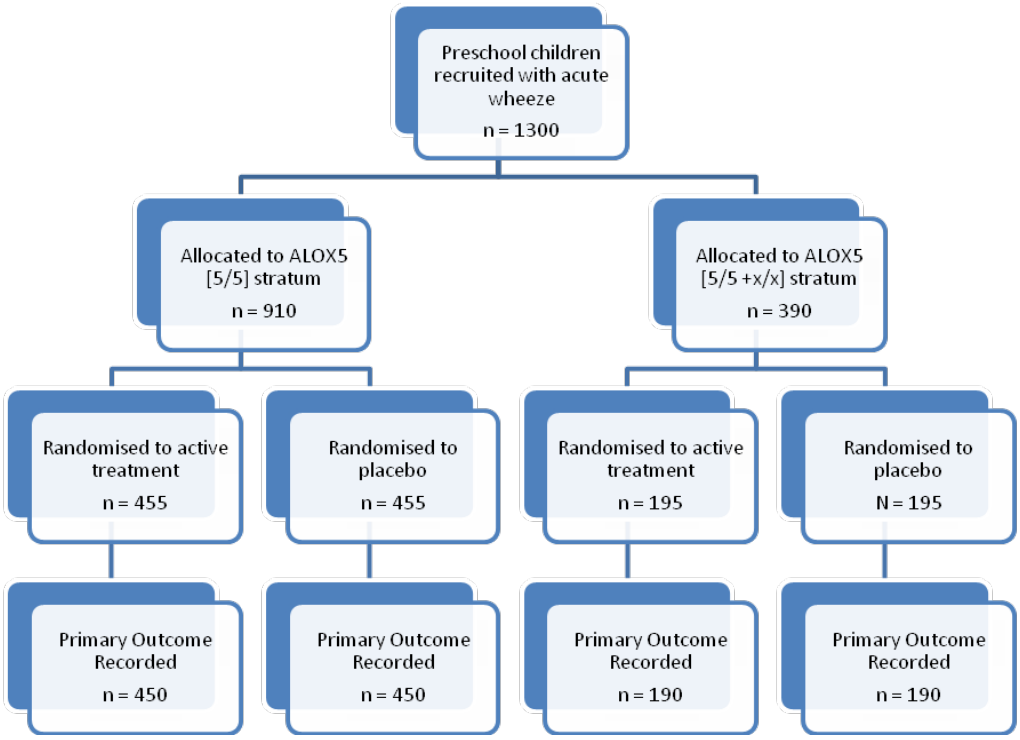
For children (participants) in each of these two genotype groups (strata) we will assign consecutive randomisation numbers from randomised permuted blocks of 10. Within each block equal numbers of children will be randomly allocated to placebo and active treatment. When all numbers from the first block have been assigned a new block of randomisation numbers will be allocated to that stratum, until a total of 1300 children in the two strata combined have been assigned a randomisation number. If a randomisation number is assigned to a child who does not subsequently take any dose of IMP, the IMP bearing that randomisation number will be returned to pharmacy, and the randomisation number may be assigned to another child (participant) provided that that medication has not been dispensed.

5.6 Flow diagrams



*Randomisation key provided by manufacturer, held in sealed envelope by Pharmacist and Data Monitoring Committee





5.7 Follow-up procedures

Parents will be contacted at the following times post-randomisation:

+Two months: **Telephone call:** a research nurse or research assistant will telephone the subject to check whether the parent has initiated the IMP, the numbers of days the IMP was used, use of healthcare resources, concomitant medications, procedures, days lost from childcare, and parent days lost from work. Parents will also be asked if their child experienced any adverse events, and these will be recorded if so.

+Four months: **Telephone call:** a research nurse or research assistant will telephone the parent to check whether the parent has initiated the IMP, the numbers of days the IMP was used, use of healthcare resources, concomitant medications, procedures, days lost from childcare, and parent days lost from work. Parents will also be asked if their child experienced any adverse events, and these will be recorded if so.

+Six months: **Telephone call:** a research nurse or research assistant will telephone the parent to check whether he/she has initiated the IMP, the numbers of days the IMP was used, use of healthcare resources, concomitant medications, procedures, days lost from childcare, and parent days lost from work. Parents will also be asked if their child experienced any adverse events, and these will be recorded if so.

+Eight months: **Telephone call:** a research nurse or research assistant will telephone the parent to check whether he/she has initiated the IMP, the numbers of days the IMP was used, use of healthcare resources, concomitant medications, procedures, days lost from childcare, and parent days lost from work. Parents will also be asked if their child experienced any adverse events, and these will be recorded if so.

+Ten months: **Telephone call:** a research nurse or research assistant will telephone the subject to check whether the parent has initiated the IMP, the numbers of days the IMP was used, use of healthcare resources, concomitant medications, procedures, days lost from childcare, and parent days lost from work. Parents will also be asked if their child experienced any adverse events, and these will be recorded if so.

+Twelve months: **Telephone call:** a research nurse or research assistant will telephone the subject to check whether the parent has initiated the IMP, the numbers of days the IMP was used, use of healthcare resources, concomitant medications, procedures, days lost from childcare, and parent days lost from work. Parents will also be asked if their child experienced any adverse events, and these will be recorded if so. Parents will be asked to return their used IMP box containing unused and used sachets.

Variable time: **Visit 3 where appropriate:** to replace expired/exhausted medications
Visit 3 in a subgroup of 30 families: A research assistant will visit the home of 30 families to establish their attitudes towards genetic testing in order to individualise therapy, acceptability of parent-initiated therapy for preschool wheeze, their experience of using the trial medication, and any difficulties/advantages of the parent-initiated approach.

Parents will contact the research nurse or research assistant at the following times post-randomisation:
Parents will be asked to contact the research nurse should they have any concerns regarding the medication, or when they are running short of medication. Data will be recorded in a follow up telephone call from the research nurse to include the number of days of wheeze, GP attendance, admission to hospital, need for additional asthma therapy, adverse events, procedures, days lost from childcare, and parent days lost from work, the nurse will request that the diary card be sent back if this has not already occurred. This researcher phonecall will not occur until at least 10 days following the parent phonecall in order not to influence the primary outcome. If a parent mislays or exhausts the IMP supplied, the research team will contact their local pharmacy with details of that child's randomisation number, and ask them to supply a replacement box of IMP containing active or placebo medication according to that subject's randomisation number. The research team shall remain blinded to active/placebo allocation.

5.8 Laboratory Assessments

Laboratory assessments of genetic polymorphisms and urinary leukotriene are specified in section 10 of this protocol will be performed according to approved standard operating procedures (SOPs).

5.9 Radiology or other Procedure

No radiological examination will be performed for study purposes. Other procedures to be performed are:

Weight:	Weight in light clothing will be measured with weighing scales and recorded in kilograms
Height	Height without shoes will be measured using a stadiometer.
Salivary sample:	Saliva for DNA will be collected using the Oragene-infant sponge system. The sponge tips are cut into an Oragene DNA kit to preserve the DNA and prevent bacterial growth. This method yields high-quality DNA and eliminates the need for traditional cheek scraping methods. ALOX5 polymorphism status will be determined within 1 week of sampling in the ICMS laboratory. DNA is extracted according to a SOP and the manufacturer's instructions (DNAgenotek). Products of the PCR are analysed by capillary electrophoresis on a 3130xl Genetic Analyser (Applied Biosystems). Fragments are obtained, varying in size depending on the copy number of the repeat sequence, and are visualized using GeneMapper v4 software. Genotypes will be called from duplicate amplifications with respect to standards run on each plate that are verified by direct DNA sequence analysis. Within 24 months of collection we will assess 150 polymorphisms in 10 genes encoding components of

the LT biosynthetic pathway and the LT receptors ALOX5, ALOX5AP, LTC4S, CYSLTR1, CYSLTR2, PLA2G4A, LTA4H, LTB4R1, LTB4R2 and MRP. These included all SNPs located in promoter regions, exons and intron-exon boundaries and the SNPs within the ALOX5AP haplotypes (referred to as Hap A and Hap B). Additional tagSNPs will be selected using the LDselect algorithm on the basis of linkage disequilibrium patterns across the genes using data from both our own previous studies in cardiovascular disease and asthma as well as resequencing data available from the Seattle SNPs and NIEHS SNPs databases. SNP genotyping will be carried out using the KASPar competitive allele-specific PCR method (Kbiosciences, Hitchin, UK).

Urine sample — A urine sample will be obtained from children in spontaneously voided urine using an age-appropriate method into a sterile receptacle. A first urine sample will be obtained when patients are well and a second during an acute wheezing illness if possible. Urinary leukotriene level will be assessed using a HPLC-mass spectrometry technique. Values will be indexed to urinary creatinine.

5.10 Unblinding procedures

At the time of generating the randomisation code described in 5.3, Nova Laboratories Ltd will also prepare 2 opaque envelopes, each containing a copy of the randomisation code detailing the active/placebo allocation associated with each randomisation number. The trial pharmacist will hold a copy of the randomisation code.

These envelopes may only be opened in the following circumstances:

1. Emergency code break:

A Principal Investigator, or physician covering for that Principal Investigator in his / her absence, may request an emergency code break in the following circumstances:

a) in case of a suspected severe adverse reaction (SAR) where knowledge of patient allocation may influence clinical management of a study participant

b) in case of a suspected unexpected severe adverse reaction (SUSAR)

c) in any other circumstance in which the PI considers that an emergency code-break is indicated

2. Non-emergency code break:

a) A Trial pharmacist will be unblinded in order to reissue medications should a subject misplace or exhaust their supply of IMP, or if their IMP supply reaches its expiry date. Other trial staff will remain blinded.

b) A general code-break will occur at the end of the trial, to allow data analysis.

5.11 Withdrawal

5.11.1 Withdrawal of Subjects

Children will be withdrawn from the study if their parents withdraw consent to participate, if their allocation is unblinded, or if an investigator concludes that this course of action is in the child's best interests. Children will also be considered to have withdrawn if their parents consistently fail to respond to telephone calls at scheduled telephonic review. They will also be withdrawn if they are commenced on regular montelukast by their usual practitioner.

5.11.2 When and How to Withdraw Subjects

Children may withdraw from the trial, or be withdrawn from the trial, in the circumstances described in section 5.11.1. If a child withdraws or is withdrawn, from the trial, the reason for withdrawal will be recorded in the case report form. When a parent fails to respond to telephone calls at scheduled telephonic review, research nurses or research assistants will make appropriate attempts to contact the parent.

5.11.3 Data Collection and Follow-up for Withdrawn Subjects

Parents of all children who withdraw prematurely from the study will be asked if they agree to continuing telephone calls as detailed in the schedule above. Data collected will be included in study analyses.

6 Investigational medicinal products

6.1 Definition of each IMP

6.1.2 Active drug

Trade name:	Singulair Granules
Composition:	4mg Montelukast sodium (which is equivalent to 4mg montelukast) granules with mannitol exipient
ATC code:	R03DC03
Pharmaceutical form:	Granules
Dosage regimen:	One sachet to be given once a day at the start of a cold or wheezy episode, and continued for 10 days.
Route of administration:	Oral
Manufacturer	Merck Sharpe and Dohme Ltd (purchased on the open market)

6.1.3 Placebo

Trade name:	Mannitol EP (Pearlitol SD 200)
Composition:	Mannitol Granules
ATC code:	Not applicable; drug master file lodged with the European Pharmacopoeia commission

Pharmaceutical form:	Granules
Dosage regimen:	One sachet to be given once a day at the start of a cold or wheezy episode, and continued for 10 days.
Route of administration:	Oral
Manufacturer	Roquette Pharma

6.2 Product sourcing, manufacture and supply

Authorisation number: MIA(IMP) 13581

Authorisation holder: Nova Laboratories Ltd., Martin House, Gloucester Crescent, Wigston, Leicestershire, LE18 4YL

6.3 Pre-medications

Not applicable.

6.4 Prescription of IMP

Trial delegation logs will specify the names of physicians authorised to prescribe IMP for this study.

6.5 Preparation and Administration of IMP

IMP will be prepared by Nova Laboratories Ltd, and shipped to pharmacy at The Royal London Hospital and additional sites. Administration of IMP is to be commenced by the parent or guardian at home at the onset of every viral upper respiratory tract infection or wheeze episode and continued for 10 days. Parents will be advised to store the IMP at room temperature, out of the reach of children, and instructed on when to initiate and stop treatment

6.6 Prior and Concomitant Therapies

Prohibited concomitant therapies are:

Montelukast granules
Treatment with another IMP

6.7 Dose modification/reduction/ delay

Administration of IMP will be discontinued in the following circumstances:

1. If the child is prematurely withdrawn from the study because their parents withdraw consent to participate.

2. If an investigator concludes that this course of action is in the child's best interests.
3. If a child is prescribed regular daily montelukast by a clinician.

6.8 Toxicity profiles

The toxicity profile of montelukast granules is minimal and is described in the SPC[12]. This will be reviewed annually and updated if relevant new data come to light.

6.9 Labelling and Packaging

IMP will be labelled and packaged by Nova Laboratories Ltd. according to principles of GMP. IMP will be packaged into white sachets.

6.10 Blinding of IMP

All the following individuals will be blinded to the IMP allocation, the parent, the child, the research nurse, the local and chief PIs. Active and placebo batches of IMP will have identical packaging, labelling and appearance.

6.11 Receipt of IMP Supplies and Storage of IMP

Participating pharmacies will inform the Chief Investigator on receipt of IMP deliveries. IMP will be stored in the pharmacy according to GCP principles.

6.12 Dispensing of IMP

Research nurses or research assistants will withdraw IMP from the participating site pharmacy on behalf of study participants on production of a signed trial prescription. Parents will be supplied with their first supply of IMP sachets at visit 2 (T0) and issued with a replacement box when that supply expires or is exhausted/misplaced.

6.13 Return and Destruction of IMP

Research nurses or research assistants will return unused or expired IMP to the participating site pharmacy where it will be destroyed according to local standard operating procedures.

7 Pharmacovigilance

7.1 General definitions

7.1.1 Adverse Events (AE)

An AE is any untoward medical occurrence in a subject (in this case "child") to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. An AE can therefore be any unfavourable and

unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of an IMP, whether or not it is considered related to the IMP. Viral respiratory tract infections and wheezing episodes that trigger IMP initiation will not qualify as AEs as their temporal relationship to IMP use is predetermined by the protocol.

7.1.2 Adverse Reaction (AR)

An AR is any untoward and unintended response in a child to an IMP, which is related to any dose administered to that subject. All adverse events judged by either the reporting investigator or the Sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

7.1.3 Serious Adverse event (SAE) or Serious Adverse Reaction (SAR)

Serious Adverse Event (SAE)

A SAE is an AE that fulfils at least one of the following criteria:

Is fatal – results in death (NOTE: death is an outcome, not an event)

Is life-threatening

Requires inpatient hospitalisation or prolongation of existing hospitalisation

Results in persistent or significant disability/incapacity

7.1.4 Suspected Serious Adverse Reaction (SSAR)

An SSAR is an adverse reaction that is classed as serious and which is consistent with the information about the medicinal product as set out in the Summary of Product Characteristics (SmPC) or Investigator's Brochure (IB) for that product.

7.1.5 Suspected unexpected Serious Adverse Reaction (SUSAR)

The definition of a SUSAR is any suspected unexpected adverse reaction related to an IMP that is both unexpected and serious. In this case the event is not outlined in the Summary of Product Characteristics (SmPC) or Investigator's Brochure (IB) for that product.

7.2 Investigators' Assessment

7.2.1 Seriousness

Responsibility for evaluation of seriousness of adverse events will be shared between the treating principal investigator and the chief investigator, according to criteria specified above.

7.2.2 Causality

Responsibility for evaluation of causality of adverse events will be shared between the treating the chief investigator and clinical co-principal investigators.

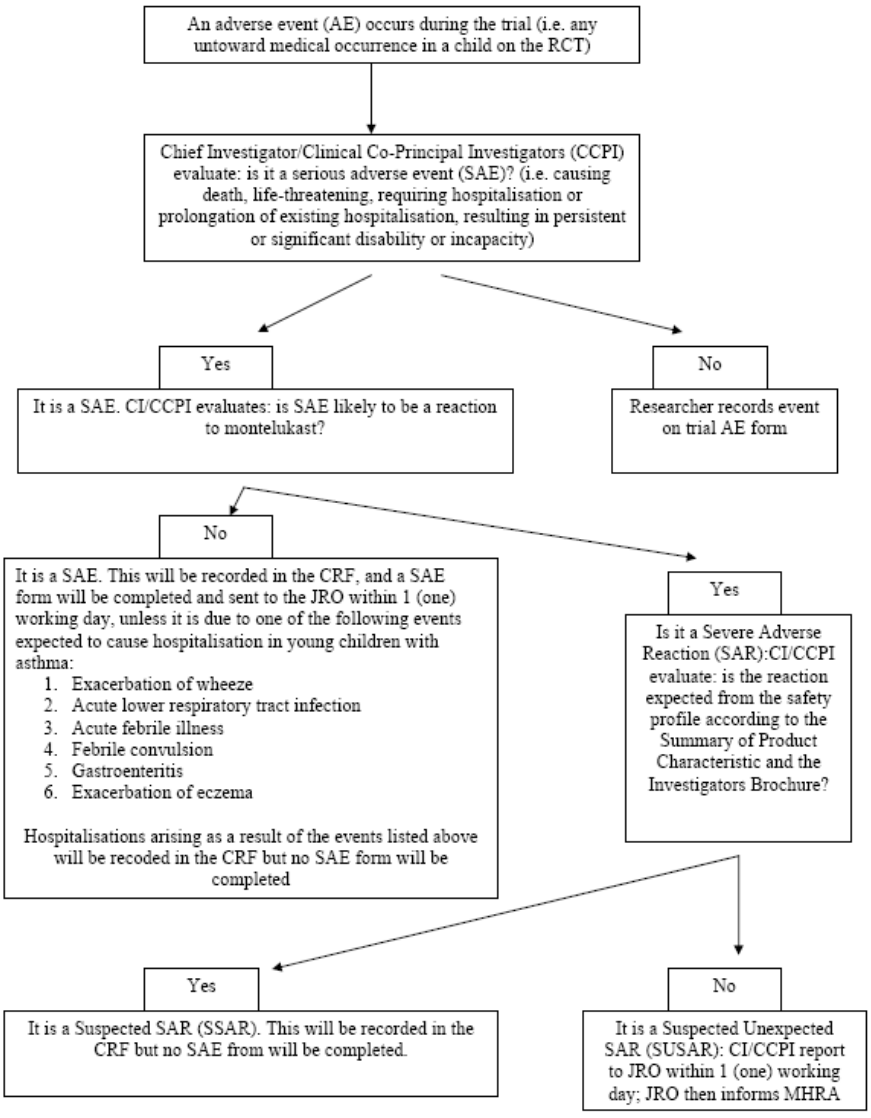
7.2.3 Expectedness

Responsibility for evaluation of expectedness of adverse events will be shared between the treating clinical co-principal investigators and chief investigator.

7.3 Notification and Reporting of Adverse Events or Reactions

Adverse events or reactions will be notified and reported according to the flowchart below.

7.3.1 Flowchart summarising procedures for notification and reporting of adverse events



7.4 Notification and Reporting of Serious Adverse Events / SUSAR

7.4.1 Recording SARs

As the IMPs used in this project are licensed in the UK, the expected SARs (outlined in the SmPC) will be recorded in the CRF. SAE forms for these SARs will not be sent to the sponsor. In addition, the population of children entered on this trial (children with at least 2 episodes of wheeze aged 10 months to 5 years inclusive at recruitment) will be expected to be hospitalised as part of their clinical care for the following reasons:

1. Exacerbation of wheeze
2. Acute lower respiratory tract infection
3. Acute febrile illness
4. Febrile convulsion
5. Gastroenteritis
6. Exacerbation of eczema

The SAEs above will be recorded in the CRF, but they will not be recorded on SAE forms or reported to the sponsor as they are classified as expected.

7.4.2 Unexpected SAEs

Unexpected SAEs will be recorded in the CRF and on the sponsor SAE form and reported to the JRO within one working day of the PI or co-investigators becoming aware of the event. The co-investigators listed in this protocol/appendix will be authorised to sign the SAE forms in the absence of the PI. SUSARs arising during the trial will be reported to the JRO and the main REC within one working day of the PI or co-investigator becoming aware of the event.

7.4.3 Annual Safety Reports (ASR)

Annual Safety Reports (ASR) will be sent by the CI to the sponsor, the MREC and the MHRA on the anniversary of the date on the “notice of acceptance letter” from the MHRA using the sponsor ASR form. The ASR will state whether new findings for the subjects of the trial have changed the benefit / risk ratio of conducting the trial.

7.4.4 Annual Progress Reports

Annual Progress Reports will be sent to the main REC and to the sponsor on the anniversary date on the MREC “favourable opinion” letter.

7.5 Procedures for reporting Blinded SUSAR

The allocation of any study participant experiencing a suspected SUSAR will be unblinded according to the WAIT Trial Standard Operating Procedure for emergency code breaking, and reported to the Sponsor. If allocation is to montelukast granules, the sponsor will report the SUSAR to the MHRA.

7.6 Expected SAEs/ SARs and non-reportable events

Expected SAEs / SARs and non-reportable events will be recorded in children's case report forms.

7.7. Pregnancy

Not applicable (preschool children only).

7.8 Overview of the Safety Reporting Process

An overview of the safety reporting process is presented in section 7.3 of this protocol.

7.9 Pharmacovigilance responsibilities

Pharmacovigilance responsibilities will be shared by the Sponsor and by the Chief Investigator and co-investigators.

8 Data Handling and Record Keeping

8.1 Confidentiality

Children's personal data will remain confidential, and will be handled, processed, stored and destroyed according to the terms of the Data Protection Act 1998.

8.2 Study Documents

Study documentation will be maintained in a Trial Master File, to be stored at the Centre for Paediatrics, Barts and The London Medical School.

8.3 Case Report Forms

Case Report Forms will include the following data: children's demographic details, medical history, concomitant medications, checklist of eligibility criteria, and records of administration of IMP.

8.4 Record Retention and Archiving

Trial records will be retained for 20 years. Records will be stored in the Centre for Paediatrics, Barts and The London Medical School while the study is being conducted, after which they will be transferred to the Barts and the London Trust archive.

8.5 Compliance

The CI & PI will ensure that this study is conducted in accordance with the latest version of the "Declaration of Helsinki" (http://www.wma.net/e/policy/b3.htm), the UK Legal Framework for Clinical Trials of Investigational Medical Products (SI 2004/1031) and subsequent relevant

amendments. The study will adhere to the principles outlined in the Guidelines for Good Clinical Practice.

8.6 Definition of the end of the study

The end of the study will be defined as the date of the final study visit of the final participant undergoing follow-up.

9 Clinical governance issues

9.1 Ethical considerations

The main ethical considerations arising from the design and conduct of this trial are as follows:

9.1.1 Rationale for research

Ethical research must be informed by existing research, and investigate an important question. We have addressed this issue by thorough review of the existing literature, and our own data showing increased leukotriene activation in preschool wheeze[5]. There is a consensus among investigators that clinical trials of parent-initiated montelukast are needed to determine whether montelukast can reduce the risk of a severe exacerbation of wheeze leading to need unscheduled medical attention.

9.1.2 Design of research

Ethical research must employ the most appropriate design in order to answer the research question. When investigating efficacy of a clinical intervention, a double blind, randomised, placebo-controlled trial is the gold standard methodology.

9.1.3 Minimisation of inconvenience, discomfort and risk for participants

Ethical research must seek to minimise potential inconvenience, discomfort and risk that children and their parents may experience during the course of a study. The principle inconveniences of the study arise from the time spent by parents to attend for the screening visit and Visit 2 where the IMP will be issued. We have sought to minimize these by providing reimbursement of reasonable travel expenses incurred as a result of participation in the study. The principle discomfort involved arises from collecting samples for DNA analysis. We have sought to minimize this by using a specially designed saliva collection system for infants (Oragene-infant DNA collection system) which does not need scraping of the buccal mucosa. The risks associated with montelukast therapy are very low, with no significant risks reported. We have sought to minimise this further by review by the data monitoring committee of accumulating data relating to adverse events.

9.1.4 Recruitment procedure

Ethical research projects should seek to recruit children from all ethnic backgrounds, and not be restricted to those fluent in the English language. To reduce misunderstandings and to maximise recruitment and adherence of ethnic minorities, the research nurse in London will

use a Sylheti interpreter when appropriate and translations of the information sheet will be available in Bengali and Gujarati (the main minority languages in Leicester and East London) at all sites where they are required.

9.1.5 Confidentiality

Ethical research projects should ensure that participants' personal data remain confidential. Our procedures for handling, processing, storage and destruction of data are compliant with the Data Protection Act 1998.

9.1.6 Data Handling and Record Keeping

Case report forms will be anonymised and held in locked filing cabinets in the local recruitment centres and in the Centre for Paediatrics, Paediatric Pragmatic Clinical Trial Section, Barts and The London School of Medicine and Dentistry. Only trial staff will have access to these.

Trial staff will enter all non-patient identifiable data from case report forms into an electronic database held on a password protected computer, linked to an ID code which will be unique for each trial participant. One electronic copy of this database will subsequently be stored on a password-protected file on the Chief Investigator's password-protected G-drive on the QMUL network; a back-up copy will be held on a password-protected file on the C drive of a stand-alone desk-top computer kept in a locked office in the Centre for Health Sciences, Barts and The London School of Medicine and Dentistry. Trial staff and representatives of the sponsor, participating NHS Trusts or regulatory authorities will be the only people with potential access to view study data that could be linked to patient identifiable data.

9.2 Summary monitoring plan

The CI will ensure that the Barts and the London monitoring template is completed in a continuous fashion throughout the study and kept up to date by the CI/co-investigators (for the first part of the report) and by the monitor to be appointed (for both the first part and the source data verification part of the template). This trial uses IMPs licensed in the UK and used within their marketing authorisation. The monitoring report will be sent to the JRO six months after the first consent form has been signed and bi-annually thereafter. The sponsor will carry out random on-site monitoring checks to ensure that the reports have been completed accurately.

9.3 Audit and inspection

Trial documentation will be made available to auditors and inspectors representing the Sponsor and the regulatory authorities.

9.4 Reporting of Serious breaches in GCP or trial protocol

Serious breaches in GCP and serious breaches of the trial protocol will be reported to the sponsor.

9.5 Quality Assurance

Data quality will be audited according to GCP guidelines, and a trail will be maintained of any change or correction to the case report form or the electronic database. The sponsor will have direct access to all trial-related sites, source data and reports in order to ensure that the trial is conducted, and data are generated, recorded and reported in compliance with the protocol and with Good Clinical Practice.

9.6 Data Monitoring Committee

A data monitoring committee (DMC) has been established for the trial. The chairman of the DMC will keep a record of DMC communications and activities. The central responsibility of this DMC will be to make recommendations to the Sponsor and the Chief Investigator on further conduct of this trial, based on results of the monitoring procedures described below. Such recommendations could include continuing or terminating the trial, or modifying its protocol. Any such modifications should not violate the concepts behind the original study protocol. If changes in the study conduct are recommended by this DMC, sufficient information should be provided to allow the sponsor and chief investigator to decide whether and how to implement them. The implementation of any DMC recommendation is the responsibility of the sponsor and chief investigator who are also free to neglect (in whole or in part) any recommendations of this DMC. The sponsor and the investigators bear the final responsibility for the conduct of the trial. This responsibility cannot be transferred to the DMC.

9.6.1 Maintenance of trial treatment randomisation codes and procedures for breaking codes.

The trial treatment randomisation code will be generated by Nova Laboratories Ltd as described above. Nova Laboratories Ltd will email a copy of this code to the Trials pharmacist at the participating sites hospital pharmacy. A member of the participating sites hospital pharmacy staff may unblind a participant's allocation at the request of a Principal Investigator, according to the WAIT Trial Standard Operating Procedure for emergency code breaking.

9.6.2 Monitoring procedures

The DMC will review accumulating data in a blinded fashion in order to monitor safety, efficacy and quality of study conduct. The DMC may also request data presented in an unblinded form.

a) Safety monitoring

The DMC may ask for an analysis to compare the incidence of fatal/life-threatening events and other SAE between the 2 groups, and report any need for changes in the conduct of the trial to the Steering Committee.

b) Efficacy monitoring

No interim efficacy analysis will is planned.

c) Monitoring quality of study conduct

If the DMC observes problems with the study conduct (e.g. with respect to protocol adherence or withdrawal of children), it should consider making recommendations to the investigators and the sponsor to improve the quality of the study.

9.6.3 Declaration of possible conflicts of interest of DMC members

The members of this DMC have no involvements that might raise the question of bias in their reports to the Trial Steering Committee in this study. Specifically, they have no financial interest in the outcome of this study, and they will not be authors on publications arising from this study.

9.6.4 Frequency and format of DMC meetings

It is anticipated that the DMC will be able to conduct all of its business by email and telephone call, rendering a physical meeting between members, investigators and representatives of the sponsor unnecessary. It is planned that the DMC will assess safety data every six months. The DMC will decide whether the frequency of monitoring needs to be changed at any point during the trial.

9.6.5 Communication Procedures

The DMC will report directly to the Trial Steering Committee.

9.6.6 Responsibilities, timelines and methodological aspects

The DMC will operate according to a charter, agreed to by all members. There will be no planned interim efficacy analysis.

9.6.7 Documentation of the DMC activities

The chair of the DMC will be responsible for ensuring the safe storage of DMC confidential reports and meeting minutes.

9.6.8 Parental Advisory Group (PAG)

Each original Centre will convene a parental advisory group consisting of at least 4 families with a child who has or had preschool wheeze and who was not recruited in the trial. Parents will guide researchers on how to approach families, will comment on the results of the qualitative interviews, and advise on how best to disseminate the trial's results. The PAG will be chaired by the local PI and will be co-ordinated by Ms Michelle Moore. Centres that are subsequently added will not be required to convene a parental advisory group.

10 Statistics

10.1 Endpoints

10.1.1 Primary endpoints

The primary outcome measure for this trial is:

- Number of times a child attends for an unscheduled medical opinion with respiratory problems over a 12 month period as confirmed from clinical records.

10.1.2 Secondary Endpoints

The secondary outcome measures for this trial are:

Respiratory morbidity

- Number of admissions to hospital over the 12 month trial period
- Duration of admissions to hospital over the 12 month trial period
- Time to first attack of wheeze
- Number of unscheduled GP consultations for wheeze
- Duration of episodes by diary card
- Severity of episodes by diary card
- Parents' overall impression of efficacy of IMP

Health service use

- Unscheduled GP consultation with exacerbation of wheeze, expressed as time from randomisation to first attendance and annual attendance rate
- A&E attendance with wheeze exacerbation, expressed as time from randomisation to first attendance and annual attendance rate
- Unscheduled hospital admission with wheeze exacerbation, expressed as time from randomisation to first admission and annual rate of admissions
- Total duration of hospital admissions for exacerbation of wheeze

Adverse events

- Severe adverse events
- Withdrawal from the trial
- Mortality due to exacerbation of asthma
- Mortality due to respiratory infection
- All-cause mortality

Medication use

- Use of oral corticosteroids, expressed as number of courses taken per year, and proportion of children receiving at least one course of oral corticosteroids during the trial
- Use of inhaled relief medication (salbutamol), expressed as mean usage per wheeze episode as recorded in diary card by parent guardian.
- Use of inhaled corticosteroids (ICS), expressed as mean daily dose of beclometasone equivalent over the 12 month trial period.
- Regular prescription of inhaled ICS over the 12 month trial period

Inflammatory outcomes

- Association between baseline urinary cysteinyl leukotriene level and:

- ALOX5 status
- Other polymorphisms of leukotriene genes
- Previous history of viral-triggered episodic and multi-trigger
- Responsiveness to montelukast
- Acute history of wheeze

Genetic parameters

- Differential responsiveness to montelukast for the primary outcome in the stratum with ALOX5 promoter polymorphism [5/5], compared with the stratum with the ALOX5 [5/x + x/x] genotype.
- Differential responsiveness to montelukast for the primary outcome resulting from other polymorphisms in genes influencing leukotriene synthesis, leukotriene metabolism and leukotriene activity.

Economic outcomes

- Costs incurred by parents due to wheeze episode (including costs of travel to health care facility, childcare, and days absence from work)
- Costs of medical care provided for exacerbation of wheeze

Qualitative outcomes (parental)

- Attitudes towards genetic testing in order to personalise therapy
- Acceptability of parent-initiated therapy for preschool wheeze
- Experience of using the trial medication
- Difficulties/advantages of the parent-initiated approach
- Views on parent information sheet

10.1.3 Study definitions

1. Need for unscheduled medical attention will be defined as an episode requiring an unscheduled attendance to either a general practitioner, or to an accident and emergency department, or a combination of both - where wheeze is diagnosed by a clinician.

2. Time from randomisation to first attack of severe wheeze will be defined as the number of days from the date of administration of first dose of IMP to the first date on which a wheeze exacerbation attains criteria of severity stated in 1 above.

3. Number of days with parent-reported wheeze will be defined as the number of days with wheeze over the 12 month trial period obtained by telephone contact with the researcher and diary card.

4. Use of inhaled relief medication, expressed as total number of occasions used over 12 month period, and mean number per wheeze episode will be obtained from the number of actuations calculated by diary card reporting.

10.2 Statistical considerations

10.2.1 Sample Size

This trial is powered to detect a clinically significant difference in the number of attacks of wheeze between intervention and control arms. We also have some power to detect differential responsiveness (in terms of the primary outcome) to montelukast in the stratum with ALOX5 promoter polymorphism [5/5], compared with the stratum with the ALOX5 [5/x and x/x]" genotype.

Baseline data on mean (0.76) and standard deviation (1.22) of number of attacks are based on data from the UK General Practitioner Research Database on courses of oral steroids (a proxy for number of episodes). These data follow an overdispersed Poisson distribution. To take account of this we used markov chain Monte Carlo simulation in WinBUGs to estimate sample sizes required: (WinBUGS Version 1.4. 2003 Available from: http://www.mrc-bsu.cam.ac.uk/bugs/welcome.shtml). To detect a 33% drop in attack rate requiring medical attention, with a power of 90% and at a significance level of 5%, and a 6% loss to follow up, we require 1050 children in total. A 33% drop in attack rates equates to an attack rate of 0.51 for the treatment group. The clinical significance of these changes is that approximately four children will need to be treated to prevent one clinically severe attack. A sample size of 1200 gives just over 80% power at the 5% significance level to detect an interaction between treatment and genotype if the effect is a 60% reduction in the [5/x plus x/x] and a 20% reduction in the [5/5] stratum. Assuming a 6% dropout, 1300 children will need to be recruited.

10.2.2 Planned recruitment rate

We plan to recruit 1300 children (participants) over 2 years.

10.3 Statistical Analysis

Poisson regression analyses will be applied to determine influence of allocation on the primary outcome and any differential response between the two strata as described below.

10.4 General considerations

Statistical analysis will be performed by a suitably qualified statistician under the supervision of Professor Eldridge.

10.5 Frequency of Analysis

Safety analyses will be conducted at 6-monthly intervals. Efficacy analyses will be conducted on termination of the trial.

10.6 Analysis of children's baseline characteristics

Following data entry and data cleaning, baseline characteristics including age, sex, and ethnic group, ongoing asthma therapy will be compared between intervention and control groups.

10.7 Analysis of primary endpoints

Initial analyses will be performed according to intention-to-treat for all participants with outcome data. Per protocol efficacy analyses will also be performed, excluding data collected after discontinuation of IMP for those participants who discontinue IMP. We will use Poisson regression with a random effect representing individuals to account for overdispersion. Fixed effects will represent the stratification factor (ALOX5 promoter) and treatment centre. The incident rate ratio (relative risk) and 95% confidence interval will be calculated. Analysis will be conducted in Stata version 10. To test for a differential effect by stratum an interaction between stratum and treatment will be fitted to this model as described in 10.8.1.

10.8 Secondary endpoint analysis

A Poisson regression analysis with a random effect for individuals to allow for over-dispersion will be applied to determine the influence of allocation on number of days with parent-reported wheeze, number of admissions to hospital, number of admissions to hospital > 4 hrs duration. An incident rate ratio for each factor will be presented with 95% confidence intervals.

Time to first attack of wheeze will be analysed using a log-rank test with adjustment for clustering and, if hazards are proportional, Cox's proportional hazards models adjusting for clustering. In a Cox model, strata and centre will be included as covariates.

Other continuous variables will be analysed with analysis of covariance. Dichotomous variables will be analysed with logistic regression analysis.

Adverse events will be analysed with descriptive statistics.

10.8.1 Genetic Analysis

To assess the difference in responsiveness to montelukast in the two ALOX5 strata we will fit an interaction term to test for the interaction between montelukast and stratum in our main model, or each treatment limb. We will also report the associations between genotype and clinical phenotype, urinary leukotriene level, and clinical outcome. To test the polymorphisms in each gene in combination, we will use a composite likelihood approach which combines the regression coefficients for all polymorphisms at each locus. Analysis of clinical effectiveness (utility) of stratification of ALOX5 status will utilise *in vitro* diagnostic multivariate index assays (IVDMIA's). We will estimate the benefits of a multivariate index assay based on our data in both clinical and economic terms (e.g. days off school days off work for parents' costs of attendance at GP and hospital, costs of treatment).

10.8.2 Pre-specified sub-group analyses

There are 2 pre-specified subgroups for analysis (other than ALOX5 genotype detailed above):

- Parent-reported history of multi-trigger vs viral episodic wheeze phenotype prior to enrolment
- Basal urinary leukotriene concentration

10.8.3 Health economic analysis

Determination of costs

Costs will be obtained by recording units of resources used, and applying tariffs to each. Important units are visits to primary care, use of out-of-hours services and A&E, prescriptions, over-the-counter drugs, hospitalisations and bed-days. Resource use will be costed using the appropriate national tariff for each type of unit cost; when unavailable, we will use the costs charged for tests carried out in the study. Unit costs for general practitioner and nurse consultations, other primary care services and outpatient attendances will be obtained from the Unit Costs of Health and Social Care 2005. These unit costs are inclusive of ancillary staff costs, overheads and training costs. Unit costs for elective and acute hospital admissions will be obtained from the Reference Costs Database. Unit drug costs per daily dose will be calculated from the Prescription Cost Analysis Database. Unit costs for diagnostic tests will be obtained from published primary costing studies conducted in the UK. Parental costs will be obtained from the telephone interview and will include time off work due to their child's wheeze and time taken to seek medical advice as well as travel expenses and out-of-pocket expenses on additional drugs. The costs associated with non-prescription drugs and visits for private health care will also be recorded. Parental time lost from work and time taken to seek medical advice due to exacerbations will be valued using age- and sex-adjusted average daily wage rates from the Office for National Statistics New Earnings Survey, 2003

10.8.3 Qualitative Analysis

We will use a constant comparison approach to ensure that new themes important to parents can be incorporated as the qualitative study progresses. Translators will be available during interviews as necessary. Transcripts will be imported into qualitative research software (MAXQDA) and analysed by a multidisciplinary team using the framework method, an established methodological approach.

10.9 Interim Analysis

Interim safety analyses will be conducted at 6-monthly intervals (as described above). Efficacy analyses will be conducted on termination of the trial.

10.10 Randomisation and Stratification

Randomisation will be stratified according to section 5.5 of this protocol.

11 Study Finances

11.1 Funding Source

This trial is funded by the National Institute of Health Research/ Medical Research Council Efficacy and Mechanism Evaluation Programme REF; 08/43/03

11.2 Subject expenses and payments

Parents will be offered reimbursement of reasonable travel expenses incurred as a result of their participation in the study.

12 Sponsorship and Indemnity

This trial will be sponsored by Queen Mary University London. The Joint Research Office for Queen Mary University/Barts and The London NHS Trust will arrange for suitable indemnity for negligent harm arising as a result of participation in this study to be in place. The protocol has been evaluated by the Governance Officer, Queen Mary and assigned an approval number 006539 QM.

13 Publication policy

Any manuscript reporting trial findings will be prepared according to CONSORT guidelines and submitted to peer-reviewed biomedical journals according to ICMJE Uniform Requirements. Authorship will be based on individuals' contribution to study design, conduct, analysis, drafting/revision of manuscript and final approval of the version to be published. Authorship will not necessarily be restricted to individuals named on this protocol; neither is authorship guaranteed to any individual named on this protocol. Contributors who do not meet authorship criteria will be listed in 'Acknowledgements'.

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15 Appendix A - Additional Sites

15.1 Secondary Care Additional Sites

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Research Nurse	Rebecca Owens	CLRN Support Manager (MCRN) Norfolk & Suffolk CLRN Level 3 East Block Norfolk and Norwich University Hospitals NHS Foundation Trust Colney Lane Norwich NR4 7UY	rebecca.owens@nnuh.nhs.uk	01603 288316	
R + D Contact					
Role	Name	Address	Email	Phone	Fax
Local PI	Dr Robert Ross Russell	Consultant Paediatrician Cambridge University Hospitals NHS Foundation Trust Hills Road Cambridge CB2 0QQ	robert.ross-russell@addenbrookes.nhs.uk	44(0)1223 586795 Bleep 07623 608360	
Research Nurse					
R + D Contact					
Role	Name	Address	Email	Phone	Fax
Local PI	Dr SC Langton Hewer MD FRCP FRCPCH	Cons Respiratory Paediatrician Bristol Royal Hospital for Children Paul O'Gorman Building Upper Maudlin Street Bristol BS2 8BJ	simon.langtonhewer@bris.ac.uk	07930 336094	
Research Nurse	Natalie Fineman	Senior Research Nurse MCRN South West Level 6 Education Centre Upper Maudlin Street Bristol BS2 8AE	mdxnf@bristol.ac.uk	0117 342 0211 0776 881 7944	
R + D Contact					
Role	Name	Address	Email	Phone	Fax
Local PI	Anne Prendiville MB BCh, MD, FRCPCH	Directorate of Child Health, 4th Floor Tower Block, Royal Cornwall Hospital Truro Cornwall TR1 3LJ	anne.prendiville@rcht.cornwall.nhs.uk	01872 252463	01872 252017
Research Nurse	Jo Webber & Hannah Solomon	Royal Cornwall Hospital Truro Cornwall TR1 3LJ	Paediatric.Research@Cornwall.NHS.UK		
R + D Contact	Scott Brown	Research & Development Directorate	Scott.brown@rcht.cornwall.nhs.uk	01872-256428	01872-256436

		The Knowledge Spa Truro, Cornwall TR1 3HD			
Role	Name	Address	Email	Phone	Fax
Local PI	Dr Greg Boden MBBCh	Neonatal Intensive Care Unit, Level 6 Maternity Unit Royal Berkshire Hospital, London Rd Reading RG1 5AN	Greg.boden@royalberkshire.nhs.uk	0118 3228125	0118 3228113
Research Nurse	Morag Zelisko BA, PGCE, RGN, RSCN	As above	Morag.zelisko@royalberkshire.nhs.uk	0118 3228652	0118 3228113
R + D Contact	Sue Hallett RN RSCN	As above	Sue.hallett@royalberkshire.nhs.uk	0118 3228652	0118 3228113

15.2 Primary Care Additional Sites - Tower Hamlets

Name	Address	Telephone number	Web address
Aberfeldy Practice	2a Ettrick Street, Poplar, London E14...	020 7515 5622	www.aberfeldypractice.nhs.uk
Albion Health Centre	333 Whitechapel Road, London E1 1BU	020 7456 9820	www.albionhealth.nhs.uk
All Saints Practice	12 Robin Hood Lane, Poplar, London E14...	020 7093 3895	www.allsaintspractice.nhs.uk
Barkantine Practice	121 Westferry Road, London E14 8JH	020 7791 8080	www.barkantine.nhs.uk
Bethnal Green Health Centre	60 Florida Street, Bethnal Green,...	020 7739 6677	www.bethnalgreenhealthcentre.nhs.uk
Blithehale Medical Centre	22 Dunbridge St, E2 6JA	020 7739 5497	www.blithehalemedicalcentre.nhs.uk
Brayford Square Surgery	5 Brayford Square, Exmouth Estate,...	0844 477 3106 or 020 7790 0802	www.varmapractice.nhs.uk
Bromley By Bow Health Centre	St Leonards Street, Bow, London E3 3BT	0844 8151020	www.eastendgp.co.uk/
Cable Street Surgery	445 Cable Street, London E1W 3DE	020 7423 9022	www.cablestreetsurgery.nhs.uk
Chrisp Street Practice	100 Chrisp Street, London E14 6PG	020 7515 4860	www.chrispstreetpractice.org
Docklands Medical Centre	100 Spindrift Avenue, Isle of Dogs,...	020 7537 1444	www.docklandsmedicalcentre.com/index.htm
East One Health	14 Deancross Street, London E1 2QA	020 7790 2978	www.eastonehealth.nhs.uk
Globe Town Surgery	82-86 Roman Road, London E2 0PJ	020 8980 3023	www.globetown.org
Gough Walk Surgery	74 Gough Walk, Canton Street, London,...	020 7515 4701	www.goughwalksurgery.nhs.uk
Grove Road Surgery	3 Ivanhoe House, 130 Grove Road, London...	020 8980 1767	www.thegroveroadsurgery.nhs.uk
Harley Grove	15 Harley Grove,	0844 815 1890	www.harleygrove.nhs.uk

Medical Centre	Bow, London E3 2AT		
Health E1	Homeless Medical Centre, 9-11 Brick...	020 7247 0090	www.healthe1practice.nhs.uk
Island Health	145 East Ferry Rd, London E14 3BQ	020 7363 1111	www.islandhealth.nhs.uk
Island Medical Centre	Roserton Street, London E14 3PG	020 7987 4231	www.islandmedicalcentre.nhs.uk
Jubilee Street Practice	368- 376 Commercial Road, London E1 0LS	0844 477 8727	www.jubileestreetpractice.nhs.uk
Limehouse Practice - Gill Street Health...	11 Gill Street, London E14 8HQ	020 7515 2211	
Merchant Street Practice	5 Merchant Street, London E3 4LJ	020 8980 3676	www.merchantstreet.nhs.uk
Mission Practice	208 Cambridge Heath Road, London, E2...	020 8983 7300	www.missionpractice.org
Pollard Row Practice	47 Pollard Row, London E2 6NA	020 7729 7942	www.pollardrowsurgery.nhs.uk
Ruston Street Clinic	Ruston Street, London E3 2LR	020 8980 1652	www.rustonstreet.nhs.uk
Spitalfields Practice	20 Old Montague Street, London E1 5PB	020 7247 7070	www.thespitalfieldspractice.nhs.uk
St Andrews Health Centre	1-3 Birchdown House, Devons Road, Bow,...	020 8980 1888	www.standrewshealthcentre.nhs.uk
St Andrews Walk-in Centre	1-3 Birchdown House, Devons Road, Bow,...	020 8980 1888	www.standrewswalkincentre.nhs.uk
St Katharine Docks Practice	12-14 Nightingale House, 50 Thomas More...	020 7488 3653	www.stkatharinedocks.nhs.uk
St Paul's Way Medical Centre	99 St. Paul's Way, London E3 4AJ	020 7538 0833	www.stpaulswaymedicalcentre.nhs.uk
St Stephen's Health Centre	Bow Community Hall, William Place,...	020 8980 1760	www.ststephenstowerhamlets.nhs.uk
Steels Lane Health Centre	384-398 Commercial Road, London E1 0LR	020 7791 3660	
Stepney Health Centre	79 Ben Jonson Road, London E1 4SA	020 7790 1059	www.stepneyhealthcentre.nhs.uk
Stroudley Walk Health Centre	38 Stroudley Walk, Bow, London E3 3EW	020 8981 4742	www.stroudleywalk.nhs.uk
Strouts Place Medical Centre	3 Strouts Place, Pelter Street, London...	020 7739 1972 or 020 7739 8859	www.stroutsplace.nhs.uk
City well being practice	129 Cannon Street Road, London E1 2LX	020 7488 4240	www.towermedicalcentre.nhs.uk
Tredegar Practice	35 St Stephen's Road, London E3 5JD	020 8980 1822	www.tredegarpractice.nhs.uk
Wapping Health Centre	22 Wapping Lane, London E1W 2RL	020 7481 9376	www.wappinggrouppractice.org
Whitechapel Health	Shah Jalal Health Centre, 44-56	020 7702 2036	www.whitechapelhealthcentre.nhs.uk

	Hessel...		
XX Place	2 Stayners Road, London E1 4AH	0844 8151020	www.eastendgp.co.uk/

15.3 Primary Care Additional Sites - Hackney

PCT	Practice name	Add1	Add2	District	Postcode
City and Hackney	Lower Clapton Group Practice	36 Lower Clapton Road		London	E5 0PD
City and Hackney	Barton House Health Centre	233 Albion Road	Stoke Newington	London	N16 9JT
City and Hackney	Stamford Hill Group Practice	2 Egerton Road	Stamford Hill	London	N16 6UA
City and Hackney	Kingsmead Healthcare	4 Kingsmead Way		London	E9 5QG
City and Hackney	Nightingale Practice	10 Kenninghall Road	Clapton	London	E5 8BY
City and Hackney	London Fields Medical Centre	38 - 44b RoadWay market		London	E8 4QJ
City and Hackney	Somerford Grove Health Centre	Somerford Grove	Stoke Newington	London	N16 7UA
City and Hackney	Richmond Road Medical Centre	136 Richmond Road		London	E8 3HN
City and Hackney	The Cedar Practice	John Scott Health Centre	Woodberry Down, Green Lanes	London	N4 2NU
City and Hackney	Beech Wood Medical Centre	86a Dalston Lane		London	E8 3AH
City and Hackney	Southgate Road Medical Centre	101 - 103 Southgate Road		London	N1 3JS
City and Hackney	The Surgery	167 Kingsland Road		London	E2 8AL
City and Hackney	Sorsby Health Centre	3 Mandeville Street		London	E5 0DH
City and Hackney	Athena Medical Centre	21 Atherden Road	Clapton	London	E5 0QP
CITY AND HACKNEY	Dalston Practice	1b Madinah Road		London	E8 1PG
CITY AND HACKNEY	Well Street Surgery	52b Well Street		London	E9 7PX
CITY AND HACKNEY	De Beauvoir Surgery	8 Englefield Road		London	N1 4LN
City and Hackney	The Lawson Practice	St Leonards	85 Nuttall Street	London	N1 5HZ
City and Hackney	The Lea Surgery	Alfred Health Centre	186 Homerton High Street	London	E9 6AG
City and Hackney	Statham Grove Surgery	Statham Grove	Stoke Newington	London	N16 9DP
City and Hackney	Queensbridge Group Practice	24 Holly Street		London	E8 3XP
City and Hackney	Heron Practice	John Scott Health Centre	Woodberry Down, Green Lanes	London	N4 2NU
City and Hackney	Elsdale Street Surgery	28 Elsdale Street		London	E9 6QY
City and Hackney	The Riverside Practice	Theydon Road Health Centre	14 Urban Hive, Theydon Road	London	E5 9BQ
City and Hackney	Wick Health Centre	200 Wick Road		London	E9 5AN
City and Hackney	Sandringham Practice	1a Madinah Road		London	E8 1PG
City and Hackney	Abney House Medical Centre	2 Defoe Road	Stoke Newington	London	N16 0EP
City and Hackney	The Surgery	74 Brooksbys Walk		London	E9 6DA
City and Hackney	Shoreditch Park Surgery	10 Rushton Street		London	N1 5DR
City and Hackney	The Surgery	6 Barretts Grove		London	N16 8AR
City and Hackney	Neaman Practice	15 Half Moon Court		London	EC1A 7HF

City and Hackney	John Scott Health Centre	Green Lanes		London	N4 2NU
City and Hackney	Clapton Surgery	148 Upper Clapton Road		London	E5 9JZ
City and Hackney	Elm Practice	1a Fountayne Road		London	N16 7EA
CITY AND HACKNEY	Cranwich Road Surgery	Flat 1 - 62 Cranwich Road		London	N16 5JF
CITY AND HACKNEY	The Hoxton Surgery	12 Rushton Street	Hoxton	London	N1 5DR
City and Hackney	Brooke Road Surgery	40 Brooke Road		London	N16 7LR
City and Hackney	Dr Shariff's Practice	Fountayne Road Health Centre	1a Fountayne Road	London	N16 7EA
City and Hackney	Allerton Road Surgery	34a Allerton Road		London	N16 5UF
City and Hackney	Latimer Health Centre	4 Homerton Terrace	Hackney	London	E9 6RT
City and Hackney	Healy Medical Centre	200 Upper Clapton Road		London	E5 9DH
City and Hackney	Trowbridge Practice	18 Merriam Avenue	Hackney	London	E9 5NE
CITY AND HACKNEY	Springfield Health Centre	19-21 Oldhill Street		London	N16 6LD
CITY AND HACKNEY	The Whiston Road Surgery	219-221 Kingsland Road		London	E2 8AN
CITY AND HACKNEY	Springfield GP-led Health Centre	19-21 Oldhill Street			N16 6LD
CITY AND HACKNEY	Drs Gadhvi, Gadhvi & Pathan	1A Fountayne Road Health Centre	Fountayne Road	London	N16 7EA