Parent-determined oral montelukast therapy for preschool wheeze with stratification for arachidonate-5-lipoxygenase (ALOX5) promoter genotype (WAIT)
Statistical Analysis Plan

Version: 2.0
Date: 18th February 2014

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*This will normally be the Trial Steering Committee (TSC) statistician, but if there is no TSC the DMC statistician may sign off the analysis plan, provided there has been no interim unblinded analysis.

INTRODUCTION

Purpose of statistical analysis plan

The purpose of this document is to provide details of the statistical analyses and presentation of results to be reported within the principal paper(s) of the WAIT trial. Subsequent papers of a more exploratory nature (including those involving baseline data only) will not be bound by this strategy but will be expected to follow the broad principles laid down in it. Any exploratory, post-hoc or unplanned analyses will be clearly identified in the respective study analysis report.

The structure and content of this document provides sufficient detail to meet the requirements identified by the International Conference on Harmonisation (ICH) and the PCTU SOP (PCTU/07).
The following were reviewed in preparation for writing this document:
Trial protocol version 7 24/06/2011
ICH E9 Guidance on statistical principals for clinical trials
ICH E3 Structure and content of clinical study reports
CONSORT guidelines for the reporting of randomised trials
PCTU_DM_04 Standard Operating Procedures (SOP) for: Data Entry, Quality Control, Data Extraction and Database lock

Members of the writing committee

Clare Rutterford (CR) was primarily responsible for (i) writing the Statistical Analysis Strategy and (ii) writing the computer code implementing the analysis strategy and (iii) implementing the strategy at the point of analysis all under the guidance of Professor Sandra Eldridge (SE).
This document has been developed prior to examination of trial data and will not be implemented prior to final approval and after the database has been locked to changes.

Summary
Changes from planned analysis in the protocol

- During November 2011 eleven WAIT participants were randomised not in accordance with the predefined schedule. The DMC recommended the inclusion of these 11 incorrectly randomized participants in the analysis and a sensitivity analysis without them included.
- Five participants were randomised with the incorrect genotype recorded at stratification and will be analysed as randomised.
- One participant AB161 was randomised and allocated a box of IMP; however they did not receive the medication and were then found to be ineligible. They shall be excluded from the analysis
- A couple of children received the wrong box of medication during the trial (approximately three doses). They shall be analysed as randomised
- A handful of participants were withdrawn prior to receiving study medication. Their study medication was reallocated to future participants. CR expressed concern whether this affected the allocation schedule that may distort the balance of the Active/Placebo blocks. Consensus was that the numbers were small so any effect will be negligible and the participants should be analysed as randomised.

STUDY OBJECTIVES AND ENDPOINTS

Study objectives

Primary objectives

1.To determine whether intermittent treatment with oral montelukast in preschool children reduces the need for unscheduled medical attention (GP visit, hospital attendance, hospital admission) for wheeze.

Secondary objectives

2.To determine whether the effect of treatment on the primary analysis is different depending upon ALOX5 status (5/5 vs. 5/x and x/x).

3.To determine whether intermittent treatment with oral montelukast in preschool children reduces the time to first medical attendance.

4.To determine whether intermittent treatment with oral montelukast in preschool children reduces the need for each type of medical attention for wheeze: hospital admissions; hospital attendance; and GP visits.

5.To determine whether intermittent treatment with oral montelukast in preschool children reduces the time to first occurrence of each type of medical attention for wheeze: hospital admissions; hospital attendance; and GP visits.

6.To determine whether intermittent treatment with oral montelukast in preschool children reduces the duration of hospital admissions.

7.To determine whether intermittent treatment with oral montelukast in preschool children reduces the number of episodes, duration and time to first event of wheeze and cold.

8.To determine whether intermittent treatment with oral montelukast in preschool children reduces the need for alternative medications (Steroids, Salbutamol).

9.To describe the safety profile of montelukast.

10.To describe parents opinion of treatment efficacy

11.To describe compliance to medication

12.To determine whether baseline urinary eicosanoid level is different across baseline groups: ALOX5 status (A or B), leukotriene genes and, type of wheeze (episodic, multitrigger). **NOTE ANALYSIS DETAIL NOT CONTAINED IN THIS PLAN**

13.To determine whether montelukast is cost effective. **NOTE ANALYSIS DETAIL NOT CONTAINED IN THIS PLAN**

Exploratory objectives

14.To determine whether the effect of treatment on the primary analysis is different depending upon ALOX5 status (categorised as (5/5 vs. 5/x) vs. x/x).

Outcome measures

Primary outcomes

The number of times a child attends for an unscheduled medical opinion (a summation of hospital admissions, attendances, GP visits,) with respiratory problems over a 12 month period as confirmed from clinical records

Secondary outcomes

Breakdown of unscheduled medical opinion
Hospital admissions:

- Number of hospital admissions over the 12 month period as recorded at each phone call
- Duration of hospital admissions as recorded at each phone call
- Time from randomisation date to date of first hospital admission as recorded at each phone call

Hospital admission for wheeze:

- Number of hospital admissions over the 12 month period as recorded at each phone call
- Time from randomisation date to date of first hospital admission as recorded at each phone call

Hospital attendance for wheeze:

- Number of hospital attendances (A&E) over the 12 month period as recorded at each phone call
- Time from randomisation date to date of first hospital attendance (A&E) as recorded at each phone call

Unscheduled GP visit for wheeze:

- Number of unscheduled GP visits over the 12 month period as recorded at each phone call
- Time from randomisation date to date of first unscheduled GP visit as recorded at each phone call

Description of wheezing episodes

Wheeze:

- Number of wheeze episodes* as recorded on the diary card
- Time to first episode* of wheeze as recorded on the diary card
- Duration of wheeze episodes* as recorded on the diary card

Cold

- Number of cold episodes* as recorded on the diary card
- Time to first episode* of cold as recorded on the diary card
- Duration of cold episodes* as recorded on the diary card

***Definition of episode of wheeze and cold: The duration of an episode is defined as the days from the start of symptoms until the last days of symptoms (includes both start and stop day) followed by a period of 5 symptom free days.**

Medication use

Steroids (OCS):

- The number of courses per year (and total number of days) as recorded on the diary card. Each mention of use on a separate diary card indicates a course.
- The proportion receiving none vs. any during the trial as recorded on the diary card or in the phonecall data.

Steroids (ICS):

- Proportion starting ICS during the trial as recorded on the diary card or phonecall data (baseline data (T2) indicates whether child was on ICS at the start of the trial)

Salbutamol:

- Total number of puffs overall per episode of wheeze as recorded on the diary card
- Total number of puffs (Salbutamol use per year)

Investigational Medicinal Product (IMP) usage:

- The number of IMP initiations (whether for wheeze or cold).
- Mean sachets (IMP use) per episode (wheeze or cold) as recorded on the diary card
- Compliance calculated from diary card, number dispensed and number returned

Inflammatory outcomes

- Baseline and exit urinary eicosanoid level
- Leukotriene genes (approximately 150 genes)

Note: this data is not stored on the main trial database and the analysis is not included within this plan

Safety outcomes

- The number of withdrawals from the trial per group
- Serious adverse events per group
- Adverse events per group
- All cause mortality per group
- Mortality due to exacerbation of asthma per group
- Mortality due to respiratory infection per group

Economic outcomes

Costs due to wheeze:
Unit costs will be assigned for the cost of medical attendances, medicines and time off work. The analysis of economic and qualitative outcomes is not contained within this analysis plan.

STUDY METHODS

Overall study design and plan

Target for randomisation: 650 intervention and 650 control participants
Date of first randomisation: 25/10/2010
Date of last randomisation: 27/12/2012
Trial design: Individually randomized, parallel group
Blinding: Participants and their treating clinician are blind to treatment allocation
Randomised Interventions: Montelukast vs. placebo
Allocation ratio: 1:1

Selection of study population

Inclusion Criteria

- age ≥ 10 months and ≤ 5 years on the day of consent.
- two or more attacks of parent-reported wheeze.
- at least one attack with wheeze validated by a clinician

- 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.

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.

Method of treatment assignment and randomisation
Randomisation was stratified according to ALOX5 promoter polymorphism status. This yielded two 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.

Children (participants) in each of these two genotype groups were assigned consecutive randomisation numbers from randomised permuted blocks of 10. Within each block equal numbers of children were randomly allocated to placebo and active treatment. When all numbers from the first block had been assigned a new block of randomisation numbers was allocated to that genotype group, until a total of 1300 children in groups 1 and 2 combined had been assigned a randomisation number. If a randomisation number was assigned to a child who did not subsequently take any dose of IMP, the IMP bearing that randomisation number was returned to pharmacy, and the randomisation number may have been assigned to another child (participant).

Treatment masking (Blinding)
This was a double-blind trial: neither subject nor investigator was aware of a subject's allocation. Active and placebo batches of IMP had identical packaging, labelling and appearance.

Sample size determination

This trial is powered to detect a clinically significant difference in the number of attacks of wheeze between intervention and control arms. We also had power to detect large differences 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.

Data on mean (0.76) and standard deviation (1.22) of number of attacks come from 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.

DATA COLLECTION

Baseline

Demographics
Height in cm
Weight in Kg
Age in years
Sex (Male; Female)
Stratum (A or B)
Ethnicity (Asian or Asian British; Mixed; Black or Black British; White; Other)
Risk factors: Birth, Atopy and Family History (Yes, No)
Preterm birth <37 wk gestation; Birth weight<2500g; Food allergy; Drug allergy; itchy rash for >6 months; Eczema; Tobacco exposure in utero; Tobacco exposure in household; daycare attendance; immunisation status for Pneumococcus; imunisation status for influenza; history of asthma mother; history of asthma father.
Pre-study illness and therapy (Yes/No)
Episodic wheeze; multitrigger wheeze; admitted to hospital in last year; ever admitted to hospital; Preventer therapy none; Preventer therapy antileukotriene; Preventer therapy Maintenance inhaled steroids; Preventer therapy episodic inhaled steroids
Age at first wheeze in months
Interval between onset of URTI and wheezing (hours)
Number of courses of systemic steroids in the last year
Number of unscheduled medical attendances for wheeze in last year
Pre-existing conditions
Medical condition
Date of diagnosis
Resolved/ongoing
Current treatment

Follow up

Unscheduled medical attendance

Phone call data: Type of attendance (A&E; Hospital; GP; Pharmacist; Other)
Phone call data: Duration of visit (calculated from date of admission and date of discharge)

Description of wheezing episodes
Diary card: Wheeze in the last 24 hours (Yes/No)
Diary card: Date of diary card entry
Diary card: Duration of wheeze episodes will be calculated where wheeze in the last 24 hours has been ticked over consecutive days
Diary card: Total duration of wheeze days over follow-up period
Medication use Steroids (OCS)

Diary card: Date
Diary card: Medication (where medication includes Prednisolone and its variations)
Diary card: Dose
Diary card: Units
Diary card: Days
Diary card: Doses per day
Phone call data: Other medications used (where medication includes Prednisolone and its variations)

Medication use Steroids (ICS)

Diary card: Date
Diary card: Medication
Diary card: Dose
Diary card: Units
Diary card: Days
Diary card: Doses per day
Phone call data: Other medications used

Medication use Salbutamol

Diary card: Date
Diary card: blue inhaler used today?
Diary card: How many times blue inhaler used?
Diary card: How many puffs when blue inhaler used?
Phone call data: Other medications used (where medication includes salbutamol and its variations)

Medication use IMP

Diary card: Date
Diary card: Wheeze in last 24 hours (Yes/No)
Diary card: Cold in last 24 hours (Yes/No)
Diary card: Trial medicine used today (Yes/No)
Phone call data: Number of IMP initiations
Phone call data: Total days used

Adverse events and serious adverse events

Clinical AE term (categorised as; minor injury, GI, URTI, CNS, minor infection, allergy, cutaneous, respiratory, haem)
SAE term
SAE expected (Yes/No)
Start date
End date
Date of death
Duration in hours
Intensity (Mild, Moderate, Severe)
Action taken (none, interrupted, discontinued, reduced)
Related to study drug (Definitely not, probably not, possibly, probably, definitely)
SAE resolved (resolved, resolved with sequelae)
Sequelae details
Outcome (improved, persisting, worsened, fatal, unknown)

Withdrawals

Withdrawal (from treatment or trial)
Date of withdrawal
Reason for withdrawal (eligibility no longer met, death of participant, other adverse event, deterioration of pre-existing condition, Poor adherence to treatment, Perceived lack of efficacy, unable to locate participant, other)
Withdrawal decision by (CI, PI, Referring investigator, Carer, Participant, other)
Permission to use data (do not use any data, use partial data up to withdrawal, use all data up to withdrawal, collect and use all follow up data)

Code broken (Yes/No)

Timing of data collection

Each child (participant) was followed up for 12 months post randomisation with data collection taking place at 2, 4, 6, 8, 10 and 12 months.

GENERAL ISSUES FOR STATISTICAL ANALYSIS

All analyses will be conducted two sided and significance interpreted at the 5% significance level.

Blinding of the statistical analysis

The statistical analysis will be conducted unblinded so that the appropriate treatment code can be used in the models fitted.

Analysis populations

Intent-to-treat population

The intention-to-treat (ITT) sample is defined for this trial as all participants randomized into the trial included in the intervention group to which they were randomised.

Available-case population

The available Case (AC) sample is defined for this trial as all participants randomized into the trial included in the intervention group to which they were randomised where outcome data are available.

Per protocol population

The Per Protocol (PP) sample is defined as the available case sample with those participants who discontinue IMP or were randomised incorrectly being excluded.

Safety population

The safety population includes all participants.

Other populations

Two populations are described for the sensitivity analyses described in section 8.5.
The first is based on the ITT population replacing any stratification factors that were incorrectly defined at randomisation with the corrected values.
The second is based on the ITT population with the exclusion of 11 incorrectly randomised participants.

Database

Description

The data were entered into and stored in a Microsoft Access database. Data were entered by trial staff who were blind to treatment group.

Data quality

Source data verification is performed for 10% of CRFs by the trial team.

Database freeze and lock

Once the trial team have completed all data entry and checking. The statistician responsible for the analysis will conduct or oversee additional data checks. These include things such as range checks, logical and consistency checks which may not be picked up by checks performed at the individual level. Procedures implemented to database lock will be followed in accordance with the relevant SOP (PCTU_DM_04 Standard Operating Procedures (SOP) for: Data Entry, Quality Control, Data Extraction and Database lock)
Analysis will take place when the database is considered final.

Analysis software
The analysis will be carried out using Stata version 12.0.

Methods for withdrawals, loss to follow-up and missing data
Those participants who withdraw and provide permission to use their data will be included in the analysis up to the point of withdrawal.

For the primary outcome phonecall data, at the time of writing (prior to unblinding) we have:
Full 12 months data on 1134/1347(84%)
29/1347 (2%) participants withdrew before the first 2 month phonecall and have no data collected as expected
12/1347 (0.9%) do not have any follow up data and this is being queried with the sites
Partial follow up data is available for 172 (13%). 44 of these participants did not formally withdraw from follow up. This is being queried with the sites
After data cleaning we expect the levels of missing data to improve. Due to these relatively low levels of missing data, and that the follow up time for each participant is to be included in the analysis no imputation of the missing data will be performed

Method for handling centre effects
We do not anticipate there to be any affect of centre and this will not be adjusted for in the analysis

Method for handling randomisation stratification or minimisation factors

The randomisation was stratified by genotype and this will be included as a covariate in all analyses.

Method for handling clustering effects
Some outcomes are collected at the level of episode, (duration of wheeze episode, duration of cold episode, duration of hospital admission) therefore we have episode data within children. In these cases a random effect is included for child.

Method for selecting other variables that will be adjusted for
All analysis will only be adjusted for genotype (see section 2.7).

Multiple comparisons and multiplicity
No formal method will be used to account for multiple comparisons. All comparisons will be defined within this document *a–priori* and all will be reported.

Method for handling non-adherence
Analysis of all primary and secondary outcomes will be performed on an intention-to-treat basis. A Complier Average Causal Effect (CACE) analysis and per protocol analysis will also be conducted for the primary analysis.

Method for handling time-varying interventions
Not applicable

Method for handling outliers and influential points
Where any outliers are identified they will be investigated to determine whether they are true recorded values or a data entry error. Where outliers are identified as a true recorded value, an assessment will be made as to whether there are clear quality indications to remove them. If such indications exist, the outliers will be removed. If such indications do not exist, the analysis will be performed both including and excluding the outlier to assess the robustness of the conclusions.

Data from external sources
Not applicable

Derived and computed variables
All derived and computed variables will be documented in the analysis programmes.
The primary outcome is a summation of all types of medical attendances across the entire trial, for each participant.
The primary outcome, and the breakdown of unscheduled medical opinion, will be taken solely from the phone call data as this data has been confirmed against clinical records.
Medication use data may be recorded on either the phone call CRF and/or the diary card. A medication will be defined as being used if it appears in either of these two records.
Medical attendance data was collected strictly within 12 months, as calculated from the date of randomisation. Participants who do not experience an event are censored at exactly 12 months of follow up or the point of withdrawal from follow up.
Any diary data collected outside of the 12 month follow up will be excluded from the analysis. Participants who do not experience episodes of cold or wheeze will be censored at the point of 12 months from randomisation or withdrawal from medication, as diary cards are not completed for those not taking IMP.

DESCRIPTIVE ANALYSES
The proposed tables to be populated during the analysis can be found in the appendix

Participant flow
Participant throughput will be summarized in a CONSORT diagram.

Representativeness of sample
Information unavailable to make this comparison

Baseline comparability of randomised groups
See table 1 in the appendix for the variables to be used in these comparisons.
Demographics
Prior and concurrent medications
Baseline and screening conditions
Baseline medical history
Baseline physical exam
Cluster characteristics if cluster randomised
Characteristics of care providers where applicable

Comparison of losses to follow-up
See table 2 in the appendix

Comparison of compliance to treatment and protocol
Compliance to treatment will be summarised as the number of returned used sachets of medication.

Emergency or accidental unblinding of randomised treatment
All unblindings will be summarised by treatment group

INTERIM ANALYSES AND SAFETY MONITORING ANALYSES

Purpose of interim analyses
No interim analyses of the data were planned or conducted.

Monitoring plan
A Data Monitoring Committee was initiated at the beginning of the study. This committee met three times during the course of the study and saw accumulating data by treatment group on recruitment, safety and efficacy. All data was presented descriptively with no hypothesis testing.

Stopping rules
Not applicable

Measures taken to minimize bias
Not applicable

Adjustment for p-values
Not applicable

Interim analysis for sample size adjustment

Not applicable

ANALYSIS OF PRIMARY OUTCOME

Definition of outcome measure

The primary outcome for each participant is the total number of unscheduled medical attendances over the course of the trial.

Descriptive statistics for outcome measure

The primary outcome will be summarised for each treatment group as the total number of events and corresponding median length of follow up time per treatment group.
Data will be presented as mean (sd) or median (interquartile range) depending upon the distribution of the data.

Primary analysis

The primary analysis will be a Poisson regression model with the follow up time of each individual fitted as an exposure variable and with a random effect for individual to account for overdispersion.
The incident rate ratio (IRR) for the treatment effect and corresponding 95% confidence interval will be presented. An IRR of less than 1 indicates a benefit of Montelukast in reducing the rate of unscheduled medical attendance needed.
Assumption checks and actions to be taken if assumptions do not hold

The fit of the model will be compared to a model without a random effect using the likelihood ratio test, and the fit will be assessed using diagnostic plots (residuals versus fitted values), alternative distributions to the Poisson such as the Negative binomial or removal of the random effect shall be considered where necessary for improved fit.
Other analysis supporting the primary (inc. sensitivity analyses)
The primary analysis will be performed on the per-protocol population and using a CACE analysis.
It will be repeated replacing any stratification factors that were incorrectly defined at randomisation with the corrected values (see section 1.4).
It will be repeated with exclusion of 11 incorrectly randomised participants (see section 1.4).

ANALYSIS OF SECONDARY OUTCOMES

Definition of outcome measure

individual type of medical attendance: (hospital admission, hospital attendance (a&e), and GP visit)
Duration (in days) of hospital admission
Number of wheeze episodes
Total duration of wheeze episode
The number of steroid (OCS) courses per year
The number of IMP courses per year
first hospital admission
first hospital attendance (A&E)
first GP visit
first episode of wheeze
proportion receiving no steroids (OCS) vs. any during the trial
Proportion starting steroids (ICS) during the trial
Salbutamol use per year
Salbutamol use per episode of wheeze per year

Descriptive statistics for outcome measure
Each outcome will be summarised for each treatment group as the total number of events or average duration of episode.

Data will be presented as mean (sd) or median (interquartile range) depending upon the distribution of the data.

Secondary analysis
The primary analysis will be repeated for each of the following secondary outcomes:
individual type of medical attendance: (hospital admission, hospital attendance (a&e), and GP visit)
Duration (in days) of hospital admission
Number of wheeze episodes
Duration of wheeze episode
The number of steroid (OCS) courses per year
The number of IMP courses per year

Time to event data will be summarised using Kaplan Meier plots. The treatment effect will be evaluated using a Cox regression model. The Hazard Ratio (HR) for the treatment effect and corresponding 95% confidence interval will be presented. A

HR of less than 1 indicates a benefit of Montelukast in reducing the time to first event.
first hospital admission
first hospital attendance (A&E)
first GP visit
first episode of wheeze

Binary outcomes will be analysed with logistic regression
proportion receiving no steroids (OCS) vs. any during the trial
Proportion starting steroids (ICS) during the trial

Assumption checks and actions to be taken is assumptions do not hold
The assumption of proportional hazards for the cox regression model will be checked using the methods proposed by Grambsch and Therneau [19]. If this assumption is violated, alternative methods will be used.
See section 8.4 for Poisson regression assumption checks.

Other analysis supporting the secondary (inc. sensitivity analyses)
None

SAFETY AND TOLERABILITY ANALYSES

Adverse event data will be summarised with descriptive statistics.

Intervention exposure
The number of participants receiving medication will be summarised per treatment group.
All Adverse events
See table 7 in the appendix
Adverse events leading to withdrawal
See table 2 in the appendix
Serious adverse events
See table 8 in the appendix
Clinical laboratory evaluations
There are no AEs defined by laboratory evaluations

SUBGROUP ANALYSES

Definition of outcome measure

For each participant, the total number of unscheduled medical attendances over the course of the trial.

Definition of subgroups

The primary analysis will be repeated to assess whether there is a differential effect of treatment by:
Genotype, categorised as 5/5 vs (5/x and x/x) and alternatively as (5/5 and 5/x) vs x/x
Whether ICS taken at baseline (yes,No)
Episodic vs multitrigger wheeze at baseline

Sample size justification for the subgroup analysis

The study has been powered to detect a specific interaction effect.

Descriptive analysis for subgroups

The mean and standard deviation of the number of unscheduled medical attendances will be summarised for each ALOX5 genotype and each treatment group

Method of analysis

The primary analysis will be repeated including an interaction term between treatment and stratum. The significance of the interaction term assessed.

AMENDMENTS TO VERSION X

REFERENCES

APPENDICES

This document was created based on the Mental Health and Neuroscience Clinical Trials Unit (MH&N CTU) analysis strategy template (version 1.5;13/02/2008)

Appendix: Statistical Analysis Report Template

CONSORT Flow Diagram

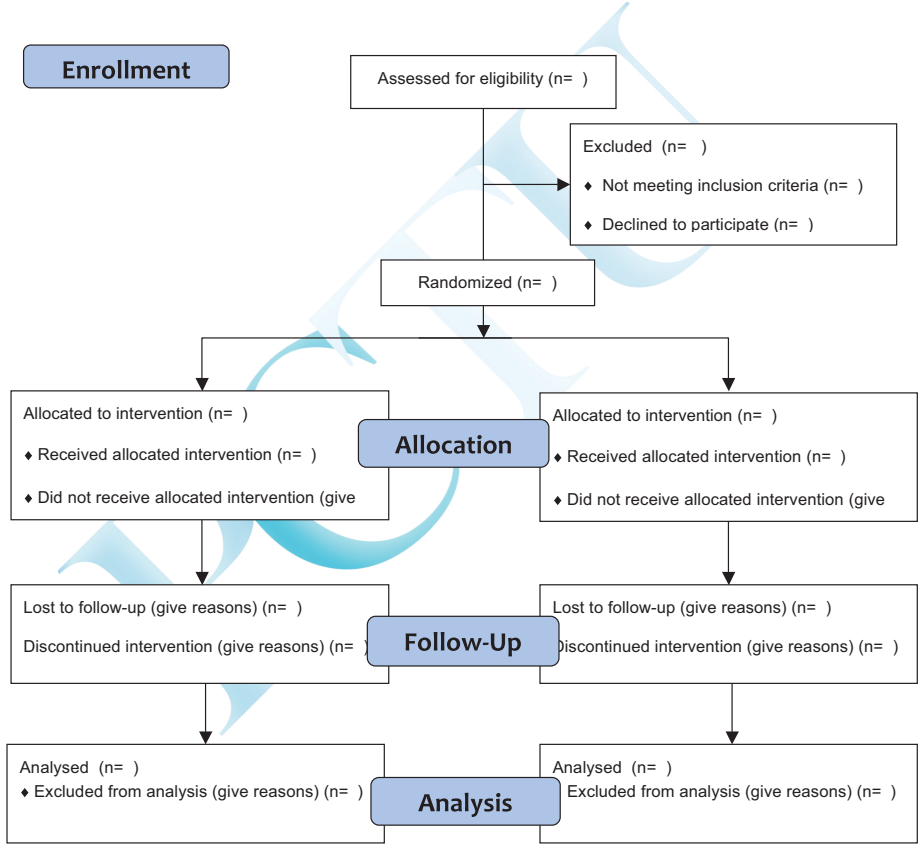

Table 1: Baseline comparability of treatment groups

ITT population	Montelukast N=			Placebo N=		
	5/5	5/x and x/x	Total	5/5	5/x and x/x	Total
Height (cm)						
Weight (Kg)						
Age (years)						
Gender						
Male						
Female						
Stratum						
A						
B						
Ethnicity						
Asian or Asian British						
Mixed						
Black or Black British						
White						
Other						
Pre existing conditions						
X						
Y						
Z						
Age at first wheeze (months)						
Interval between onset of URTI and wheezing (hours)						
Episodic wheeze						
Multi-trigger wheeze						
Admitted to hospital in last year						
Admitted to hospital ever						
Preventer therapy						
None						
Antileukotriene						
Maintenance inhaled steroids						
Episodic inhaled steroids						
Risk factors						
Preterm birth <37 wk gestation						
Birth weight<2500g						
Food allergy						
Drug allergy						
Itchy rash for > 6 months						
Eczema						
Tobacco exposure in utero						
Tobacco exposure in						

household	
Daycare attendance	
Immunised for Pneumococcus	
Immunised for influenza	
History of asthma in mother	
History of asthma in father	
Numbers are N(%) or mean (SD)	

This table is to be repeated for the alternative stratification (5/5 and 5/x) versus (x/x).

Table 2: losses to follow up

ITT population	Montelukast N=			Placebo N=		
	Trial	Treatment	Total	Trial	Treatment	Total
Reason for withdrawal						
Eligibility no longer met						
Death						
Other adverse event						
Deterioration of pre-existing condition						
Poor adherence to treatment						
Perceived lack of efficacy						
Unable to locate participant						
Other						
Decision made by						
CI						
PI						
Referring investigator						
Carer						
Participant						
Other						
Permission to use data						
Do not use any data						
Use partial data up to withdrawal						
Use all data up to withdrawal						
Collect and use all follow up data						
Numbers are N (%)						

Table 3 Primary analysis: unscheduled medical attendances for wheeze over 12 months

ITT population	Montelukast N=	Placebo N=	Adjusted IRR (95% CI)[1]	p-value
Follow up time (days)				
Number of :				
Any medical attendance				
All				
Straum A				
Stratum B				
Stratum 5/5 and 5/x				
Stratum D x/x				

	ICS at baseline Multitrigger vs episodic wheeze
Hospital admissions	
Hospital attendances (A&E or admission)	
Unscheduled GP visits	
Parents considered medication to be efficacious, N(%)	

Data are mean (SD)

[1] Data are analysed using Poisson regression with fixed effects for stratification factor and treatment group a random effect for individual to account for overdispersion with follow up time fitted as the exposure. An interaction term has been included to assess whether there is a differential treatment effect dependent on stratum.

Table 4: Episodes of cold and wheeze

ITT population	Montelukast N=	Placebo N=	IRR (95% CI)[1]	p-value
Number of:				
Wheeze episodes				
Cold episodes				
Days wheezing				
Returned used medication sachets				
Duration of:				
Wheeze episodes (days)				
Hospital admission (days)				

Data are mean (SD)

[1] Data are analysed using Poisson regression with fixed effects for stratification factor and treatment group a random effect for individual to account for overdispersion with follow up time fitted as the exposure. Duration of each hospital admission is analysed using Poisson regression with fixed effects for stratification factor and treatment group a random effect for individual with follow up time fitted as the exposure.

Table 5: Time to first event of unscheduled medical attendance, wheeze or cold

ITT population **Time (in days) to first:**	Montelukast N=	Placebo N=	HR (95% CI)	p-value
Hospital admission				
Hospital attendance (A&E or admission)				
Unscheduled GP visit				
Episode of wheeze				
Episode of a cold				

Data are median (IQR)

Data are analysed using a Cox regression model with fixed effects for stratification factor and treatment group

Table 6: Medication usage

ITT population	Montelukast N=	Placebo N=	IRR or OR (95% CI)	p-value
Steroids (OCS)				
[1]Number of courses, mean (SD)				
[2]Proportion receiving OCS, N (%)				
Steroids (ICS)				
[2]Proportion starting, N (%)				
Salbutamol				
[1]Number of puffs used per episode, mean(SD)				
Total puffs used per year				
Investigational Medicinal Product				
[1]Number of initiations, mean (SD)				
[1]Number of sachets per episode, mean (SD)				
Number of sachets used per year				

[1]Data are analysed using Poisson regression with fixed effects for stratification factor and treatment group and a random effect for individual to account for overdispersion with follow up time fitted as the exposure.
[2] Data are analysed using logistic regression with fixed effects for stratification factor and treatment group

Table 7 Total adverse events per group

Safety population	Montelukast N=	Placebo N=
All events		
Minor injury		
GI		
URTI		
CNS		
Minor infection		
Allergy		
Cutaneous		
Respiratory		
Haem		
Possibly, probably or definitely related		
Minor injury		
GI		
URTI		
CNS		
Minor infection		
Allergy		
Cutaneous		
Respiratory		
Haem		
Data are n (%)		

Table 8: Serious Adverse events per group

Safety population	Montelukast N=	Placebo N=
Death		
XXX		
XXX		
...		
Data are n (%)		