Portsmouth Hospitals NHS
NHS Trust

laser
A breath of fresh air in asthma

Laminar **A**irflow in **S**evere Asthma for **E**xacerbation **R**eduction

A multi-centre randomised, double blind, placebo-controlled, parallel group trial of the effectiveness of the nocturnal use of a Temperature Controlled Laminar Airflow (TLA) Device (Airsonett®) in adults with poorly-controlled, severe allergic asthma

Date and Version No: 23/06/2015 Version 5.0

HTA Reference 12/33/28

REC Reference::	14/SC/0092
ISRCTN:	**ISRCTN46346208**
Chief Investigator:	Professor Anoop J Chauhan
Trial Design Team	Prof P H Howarth, University Hospitals Southampton NHS Foundation Trust Prof P Bradding, University Hospitals of Leicester NHS Trust Dr A Mansur, Heart of England NHS Foundation Trust Prof T Dean, University of Portsmouth Dr N Rahman, University of Oxford Ms L Yu, Centre for Statistics in Medicine, Oxford University Dr R Luengo-Fernandez, Health Economics Research Unit, Oxford University Dr A Dewey, University of Portsmouth Ms C Fogg, RDS South Central, University of Portsmouth Mrs E Munro, Portsmouth Hospitals NHS Trust Dr T Brown, Portsmouth Hospitals NHS Trust Dr W Storrar, Portsmouth Hospitals NHS Trust (Trial Co-ordinator)
Patient Representatives:	Mr K Boughton, Mr K Manship, Mrs S Willsher
Sponsor:	Portsmouth Hospitals NHS Trust
Funder:	NIHR Health Technology Assessment Programme

Signatures:

Professor AJ Chauhan Chief Investigator	Ms K Greenwood Sponsor Representative

TABLE OF CONTENTS

1. AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
Minor 1	2.0	20/03/2014	Will Storrar	Grammar and spelling
Minor 2	3.0	07/08/2014	Will Storrar	Vitalograph ASMA-1 USB device removed.
Minor 3	4.0	23/10/2014	Will Storrar	Removal of 12 month limit on historical bronchial challenge test results
Major 1	5.0	28/05/2015	Anoop J Chauhan / Will Storrar	3 amendments to trial inclusion criteria: 1. Reduction in lower age for participation from 18yrs to 16yrs. 2. Reduction in the length of the pre-screening stability period from 4 weeks to 2 weeks. 3. Reduction in the required inhaled corticosteroid (ICS) dose from >1000 BDP or equivalent to ≥1000 BDP or equivalent

Department of Health Disclaimer:

The views and opinions expressed herein are those of the authors and do not necessarily reflect those of the HTA, NIHR, NHS or the Department of Health.

2. ABBREVIATIONS

ACD	Asthma Control Diary
ACQ	7-Point Asthma Control Questionnaire
AC-QOL	Adult Carers Quality of Life Questionnaire
ADE	Adverse Device Effect
AE	Adverse Event
AQLQ(S)	Standardised Asthma Quality of Life Questionnaire
ATS/ERS	American Thoracic Society/European Respiratory Society
BDP	Beclomethasone Dipropionate
BMI	Body Mass Index
BNF	British National Formulary
BTS/SIGN	British Thoracic Society/Scottish Intercollegiate Guidelines Network
CE	Conformité Européenne
COMET	Core Outcome Measures in Effectiveness Trials
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CPAP	Continuous Positive Airway Pressure
CRF	Case Report Form
DSMC	Data Safety Monitoring Committee
DVD	Digital Versatile Disc
ED	Emergency Department
EOS	End of Study
EQ5D-5L	EuroQol 5-Dimension 5-Level Questionnaire
F_ENO	Fractional exhaled Nitric Oxide
FDP	Fluticasone Dipropionate

FEF_{25-50}	Forced Expiratory Flow Rate (25-50%)
FEV_1	Forced Expiratory Volume (in 1 second)
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GETE	Global Evaluation of Treatment Effect
GINA	Global INitiative for Asthma
GP	General Practitioner
HDM	House Dust Mite
HES	Hospital Episode Statistics
HERC	Health Economics Research Centre
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
ICS	Inhaled Corticosteroid
IgE	Immunoglobulin-E
ITT	Intention To Treat
ITU	Intensive Treatment Unit
IU/L	International Units/Litre
LASER	Laminar Airflow in Severe asthma for Exacerbation Reduction
MART	Maintenance and Reliever Therapy
MHRA	Medicines and Healthcare products Regulatory Agency
MI	Multiple Imputation
NHS	National Health Service
NIV	Non-Invasive Ventilation
OCS	Oral Corticosteroid
ORTU	Oxford Respiratory Trials Unit (Respiratory division of OCTRU)
OCTRU	Oxford Clinical Trials Research Unit

PC_{20}	Provocation Concentration causing 20% drop in FEV_1
PEF	Peak Expiratory Flow
PHT	Portsmouth Hospitals NHS Trust
PI	Principal Investigator
PIS	Patient Information Sheet
PSSRU	Personal Social Services Research Unit
QALY	Quality-Adjusted Life Year
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
R&D	Research and Development
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SEK	Swedish Krona
SMP	Self-Management Plan
SNOT-22	22-item Sino-Nasal Outcome Test
SPT	Skin Prick Testing
TLA	Temperature-Controlled Laminar Airflow
TMG	Trial Management Group
TSC	Trial Steering Committee
TSP	Trial Specific Procedure
UADE	Unanticipated Adverse Device Event
USADE	Unanticipated Serious Adverse Device Effect
VoI	Value of Information
WHO	World Health Organisation
WPAI(A)	Work Productivity and Activity Impairment (Asthma)
WPAI(CG)	Work Productivity and Activity Impairment (Care-Giver)

3. SYNOPSIS

Study Title	**A multi-centre randomised, double blind, placebo-controlled, parallel group trial of the effectiveness of the nocturnal use of a Temperature Controlled Laminar Airflow (TLA) Device (Airsonett®) in adults with poorly-controlled, severe allergic asthma; the LASER Trial.**
HTA Reference	12/33/28
Aim	To ascertain whether home-based nocturnal TLA usage over a 12 month period can reduce exacerbations and improve asthma control and quality of life as compared to placebo, whilst being cost-effective and acceptable to adults with poorly-controlled, severe allergic asthma.
Study Design	A multi-centre randomised double-blind placebo-controlled parallel group trial design.
Population	Adults (16-75 years) with severe, poorly-controlled asthma despite high intensity treatment who are sensitised to a perennial indoor aeroallergen.
Intervention	Nocturnal home-based TLA treatment using an Airsonett® device, in addition to standard care in accordance with the national BTS/SIGN Guidelines for the management of asthma in adults. The device is CE marked for use in asthma.
Comparator	A trial-validated placebo device that mimics the intervention in all aspects, other than delivering the laminar airflow away from the breathing zone, in addition to standard care in accordance with the national BTS/SIGN Guidelines for the management of asthma in adults.
Planned Sample Size	222 participants are required to detect a 25% reduction in the rate of severe asthma exacerbations in the treatment group modelled on a baseline rate of 2 severe exacerbations per year (see Appendix 1) and incorporating a loss-to-follow-up rate of 10%.
Randomisation	Participants will be randomised 1:1 to TLA therapy or placebo using a validated computer randomisation program with a minimisation algorithm to ensure balanced allocation of patients across the two treatment groups for clinical site, prevalent vs. incident cases and the following prognostic factors at baseline: Exacerbation frequency in the previous 12 months, use of maintenance oral corticosteroids and pre-bronchodilator FEV_1.
Follow-up duration	12 months
Internal Pilot	An internal pilot will be conducted over the first 4 months of trial recruitment at the 5 initial trial recruitment sites to evaluate trial processes and the retention of trial participants.

Primary Outcome	The frequency of severe asthma exacerbations occurring within the 12 month follow-up period. Severe asthma exacerbations are defined in accordance with ATS/ERS guidelines as a worsening of asthma requiring systemic corticosteroids, ≥30mg prednisolone or equivalent daily (or ≥50% increase in dose if maintenance 30mg prednisolone or above) for 3 or more days. Courses of corticosteroids separated by ≥7 days will be treated as separate severe exacerbations.
Secondary Outcomes	Secondary outcomes include changes in asthma control, lung function, asthma-specific and global quality of life for participants and their carers, adherence to intervention, healthcare resource use and costs, and cost-effectiveness.
Data Collection	Participants will report severe exacerbations to their local site trial team as soon as possible throughout the follow-up period. An exacerbation diary completed by participants from the onset of an exacerbation will be used by site-teams to corroborate severe exacerbations. Lung function, quality of life, symptom scores composite asthma control scores and adherence data will be assessed at hospital visits at 3, 6, 9 and 12 months from randomisation and quality of life for carers at 12 months. Participants will be invited to attend focus groups, held within 4 weeks of completing their 12 month follow-up period, to obtain data about experience of the device. Healthcare resource use information will be collected from the participant, GP and hospital records, as well as data on the social impact of asthma to facilitate cost-effectiveness analyses.
Statistical Analysis	The principal comparisons will be performed on an intention-to-treat basis. Analysis of exacerbation rate at 12 months from randomisation will be analysed using a generalised linear model (with Poisson distribution or negative binomial distribution depending on the dispersion of the data), adjusting for minimisation factors. A linear mixed effect model will be used for analysis of all continuous secondary outcomes with repeated measures. Chi-square test will be used for categorical data.
Timetable	Total duration 42 months – Month 1-6: set-up. Month 7-24 recruitment (with 4-month internal pilot). Months 25-37: 12 months follow-up to study close. Month 38-42: analysis, write-up and dissemination.

4. SCHEDULE OF PROCEDURES

Study Visit	1	2			3	4	5	6
	Screening Period			Treatment Period				
Study Procedures	**Screening**	**Randomisation**		**1 Month**	**3 Months**	**6 Months**	**9 Months**	**12 Months**
Participant Procedures								
Informed Consent[i]	X							
Demographics/Medical History	X							
Asthma History	X							
Asthma Review	X				X	X	X	X
Inclusion/Exclusion Criteria	X	X						
Post-Randomisation Telephone Review[ii]				X				
Severe Exacerbation Reporting								
Severe Exacerbation Reporting[iii]	→							
Questionnaires								
ACQ	X	X			X	X	X	X
AQLQ(S)		X			X	X	X	X
EQ-5D-5L		X			X	X	X	X
SNOT-22		X			X	X	X	X
WPAI(A)		X			X	X	X	X
Indoor Air Quality Questionnaire		X						
GETE								X

Study Visit	**1**	**2**			**3**	**4**	**5**	**6**
	Screening Period			**Treatment Period**				
Study Procedures (Participant contd.)	**Screening**	**Randomisation**		**1 Month**	**3 Months**	**6 Months**	**9 Months**	**12 Months**
Lung Function Tests								
Spirometry	**X**	**X**			**X**	**X**	**X**	**X**
Reversibility testing	**X**							**X**
F_ENO		**X**			**X**	**X**	**X**	**X**
Allergy Testing								
Skin Prick Tests or Serum Specific IgE[iv]	**X**							
Blood tests (Total IgE/Eosinophil Count)	**X**							
Asthma Control Diary & Electronic PEF Diary								
Issue / Training	**X**	**X**			**X**	**X**	**X**	
Asthma Control Diary & Electronic PEF Diary		**-2Wks**			**-2Wks**	**-2Wks**	**-2Wks**	**-2Wks**
LASER Diary								
LASER Diary Completion				→	→	→	→	→
LASER Diary Review					**X**	**X**	**X**	**X**
Device Usage Data								
Participant Reported Device Usage Data					**X**	**X**	**X**	**X**
Resource Use								
Healthcare Resource Use					**X**	**X**	**X**	**X**
Informal Care Requirements					**X**	**X**	**X**	**X**
Qualitative Study								
Device Acceptibility Focus Group								**X**

Study Visit	1	2			3	4	5	6
	Screening Period			Treatment Period				
Study Procedures (Participant contd.)	Screening	Randomisation		1 Month	3 Months	6 Months	9 Months	12 Months
Post-Trial Provision Period[v]								
Post-Trial Provision Period Offered								X
Partner Procedures[vi]								
Informed Consent		X						
Device Acceptability Focus Group								X
Carer Procedures[vi]								
Informed Consent		X						
AC-QOL Questionnaire		X						X
WPAI(CG) Questionnaire		X						X
Study Device Procedures								
Installation[vii]			X					
Filter Change						X		
Device Reported Usage (Engineer reading)						X		X
Exchange / Removal[viii]								X

i. Informed Consent will be sought for the main trial and qualitative studies (during internal pilot and at completion of the follow-up period) at Screening Visit 1
ii. Post Randomisation Telephone Review after 1 month (+/- 3 days) to review device usage and check device related technical issues have been addressed
iii. Severe Exacerbation Reporting. Participants will report severe exacerbations to their local trial team as soon as possible throughout the follow-up period
iv. Serum Specific IgE only required if Skin Prick Tests not available
v. Post-Trial Provision Period refers to treatment with an active TLA device free of charge including filters and technical support over a 4 year period
vi. Adult Carer / Partner participation in selected cases is entirely optional and will not influence participant's eligibility for inclusion in the trial
vii. Installation within 10 working days of Randomisation
viii. Device Exchange / Removal within 10 working days of last study visit or focus group involvement whichever comes last

5. LAY SUMMARY

5.1 The Problem

'People don't see me or understand when I've cried and wept and punched my fist through the wall gasping for another breath, thinking I'm not going to be able to make it this time. I feel like I am going to die' (Mike Liddel-Taylor, Bury St Edmunds; Living on a Knife Edge, Asthma UK).

Asthma affects over 5 million patients in the UK. Half a million of them have a severe form of asthma and are disabled by frequent and potentially life-threatening asthma attacks (or 'exacerbations') that cannot be prevented by their usual treatment. Attacks devastate the lives of patients, often leading to frequent hospital stays and repeat courses of strong medicines such as steroids that can lead to long-term harmful effects. The disease affects all aspects of life for the patient and their family and often leads to problems such as depression and unemployment. Severe asthma is costly to the NHS, accounting for 80% of the total costs of treating asthma (over £1 billion/year). Despite NHS strategy to improve management of long-term conditions, current treatments for severe asthma are limited, with a lack of research upon which to base treatment decisions, and a significant unmet need for newer treatments.

5.2 A New Treatment

We will test whether a new machine that reduces the number of allergy particles in the air (which cause asthma) can reduce these debilitating asthma attacks and improve patients' quality of life.

The machine is known as a 'Temperature Controlled Laminar Airflow (TLA)' device, and remains at the patient's bedside and switches on automatically every night, requiring no masks or other uncomfortable equipment, and is very safe and easy to use. The device works by filtering out the allergy particles in the air of the patient's breathing zone, allowing the patient's lungs and airways to 'rest' in clean air overnight.

This TLA device has been shown to be safe for patients and effective in reducing symptoms of asthma. We now need to explore in a larger trial whether the treatment can reduce asthma attacks and asthma symptoms, such as coughing and wheezing. We will assess whether using the machine in the NHS would be cost-effective and acceptable for patients.

5.3 The Trial

We will include 222 adults, half of whom will be given a TLA device that is working, and the other half will be given a device which has been inactivated (the filtering process will be switched off, although the participants will not be able to tell that this has occurred). Which participant receives the working or deactivated device will be decided by a random process and will be unknown to the researcher and the participant. An engineering team from the manufacturer will install the device in the participants' home at the beginning of the study and be available throughout the study period to deal with any queries.

All participants will continue receiving their usual treatments. Participants will be in the study for 12 months, and will report their asthma attacks to the trial team whenever they occur during this period. In addition, they will visit the trial team 4 times (after 3, 6, 9 and 12 months) to assess their asthma control and quality of life. At the end of the trial, we will invite participants at each site to join a group discussion

where researchers will explore the participant's thoughts about the TLA device. At the end of their participation in the trial, all participants who have used the device for more than 6 months, regardless of their initial study group, will be offered the opportunity to keep an active device in their home free of charge for a further four years.

6. BACKGROUND AND RATIONALE

6.1 The Burden of Severe Asthma

6.1.1 Epidemiology

Asthma affects over 5.4 million people in the UK with nearly 500,000 experiencing severe symptoms and frequent exacerbations that are inadequately controlled with available treatments.[1,2] The burden of severe asthma on the NHS is enormous accounting for 80% of total asthma cost (£1 billion[3]) with frequent exacerbations and expensive medications generating much of this cost.[4] In 2009 there were 1131 deaths due to asthma[5], with those whose asthma remains poorly-controlled facing the greatest risk.[6,7] Patients with severe asthma bear the greatest burden of asthma morbidity. They experience more frequent and severe exacerbations[8] which reduce their quality of life, impair their ability to work and place an enormous burden of anxiety on them and their families.[9] There is also an increased risk of significant depression.[10] 1in 5 asthmatics in the UK report serious concerns that their next asthma attack will kill them.[1] As highlighted in the 2010 Asthma UK report 'Fighting for Breath' these patients also face discrimination from employers, healthcare professionals and society as a whole as a result of their asthma.[11]

6.1.2 The Unmet Need in Severe Asthma

Current treatments including oral corticosteroids, 'steroid-sparing' immunosuppressants and monoclonal antibody therapies are often of limited efficacy and have potentially serious side effects (steroids, immunosuppressive agents) or are prohibitively expensive (monoclonal antibodies). The adverse effects of long-term oral steroids include adrenal suppression, decreased bone mineral density, diabetes and increased cardiovascular mortality.[12] The anti-IgE treatment Omalizumab® has been shown to reduce exacerbations by up to 50%[13] and improve quality of life in severe allergic asthma but costs up to £26,640 per year,[14] which is substantially more than the current annual rental cost of a TLA device (£2,088). The National Institute for Health and Clinical Excellence reappraised the use of Omalizumab® in 2012 and, whilst recognising the grave effects of severe uncontrolled asthma on quality of life for patients and their families, have concluded that this is only cost-effective within the NHS, by restricting its use to those experiencing 4 or more severe exacerbations in the preceding 12 months.[14] These patients are left with a significant unmet clinical need and a specific requirement for therapies which reduce systemic steroid exposure.

It is also important to acknowledge the often unrecognised role that carers play in looking after patients with, poorly-controlled severe asthma. The 'Fighting for Breath'[11] document also highlighted the problems faced by asthma carers and the strain this can place on their physical and mental health. In addition, having to take time off work, work part-time or not being able to work at all as a result of the patient's care needs places a significant financial burden on to carers.

6.1.3 National/International Strategies to Improve Asthma Care

The Department of Health Outcomes Strategy for COPD and Asthma (2011) recognised the huge burden that poorly-controlled asthma places on people's lives and the NHS, and spelt out the political

commitment to improve asthma control and reduce asthma related emergency healthcare needs and deaths.[15] The 2011 British Thoracic Society (BTS) and Scottish Intercollegiate Guidelines Network (SIGN) national asthma guidelines[16] and 2010 WHO consultation on severe asthma[8] have highlighted an urgent need for research in severe asthma, acknowledging the limitations of available treatments in severe asthma and the dearth of clinical trials upon which to base management recommendations. Asthma UK emphasised in its research strategy for 2012 document that new therapies able to reduce symptoms and prevent exacerbations will improve clinical outcomes and patient well-being and reduce the cost of treating severe asthma within the NHS.

6.2 The Significance of Allergen Exposure and Environmental Interventions

More than 70% of severe asthmatic patients are sensitised to common aeroallergens and/or moulds,[17] and the level of allergen exposure determines symptoms; those exposed to high allergen levels are at increased risk of exacerbations and hospital admissions.[18,19,20,21] Domestic exposure to allergens is also known to act synergistically with viruses in sensitised patients to increase the risk and severity of exacerbations.[22] Allergen avoidance has been widely recognised as a logical way of treating these patients.[23] In controlled conditions, long-term allergen avoidance in sensitised asthmatics reduces airway inflammation with consequent symptomatic improvement, further supported by high-altitude, clean-air studies.[24,25,26] Unfortunately, effective methods of allergen reduction have proved elusive[27,28] with current measures unable to reduce allergen load sufficiently to yield a consistent clinical improvement, thus leaving a significant gap in the potential strategies for reducing asthma severity through allergen reduction.

6.3 Rationale for Temperature Controlled Laminar Airflow (TLA) Therapy

At night airborne particles are carried by a persistent convection current established by the warm body, transporting allergens from the bedding area to the breathing zone.[29] Proof-of-concept studies have shown the TLA device reduces the total number of airborne particles >0.5µm in the breathing zone by 3000-fold ($p<0.001$), cat allergen exposure by 7-fold ($p=0.043$) and significantly reduces the increase in particles generated when turning in bed for all particle sizes.[30] When compared to a best in class traditional air cleaner TLA is able to reduce exposure to potential allergens by a further 99%.[30] We postulate that this highly significant reduction in nocturnal exposure, targeted to the breathing zone, explains why TLA may succeed in an area where so many other measures, including air filters, have failed.

6.4 Evidence of Benefit with TLA Therapy

The TLA device when compared to placebo, has proven efficacy on asthma-related quality of life and bronchial inflammation (measured by exhaled nitric oxide) in a pan European multicentre Phase III study,[31] (n=282, age range 7-70 years). The greatest benefit was seen in the more severe asthma patients requiring higher intensity treatment (GINA Steps 4-5) and in patients with poorly controlled asthma (Asthma Control Test <19). GINA Steps 4-5 are consistent with ATS/ERS Severe Asthma Guideline definitions 2013[32] and BTS/SIGN Guideline treatment Steps 4-5 (inhaled corticosteroid dose ≥1000µg/day beclomethasone (BDP) equivalent plus an additional controller medication such as a long acting ß2-agonist, leukotriene receptor antagonist or a sustained release theophylline). Whilst not powered to ascertain an effect on exacerbations, a post-hoc analysis showed a decreased exacerbation rate in more severe patients treated with TLA when compared with placebo with a trend towards significance (mean 0.23 TLA; 0.57 placebo $p=0.07$). A cost-effectiveness analysis based on the results from this trial also found no significant differences in ED visits, hospitalisation days, medication usage, and therefore overall costs between the two study groups.[33] This lack of significant findings probably reflected the fact that the trial was not powered to detect differences in exacerbations, a predictor of increased asthma healthcare

resource use and costs.[34] Despite the lack of a significant reduction in healthcare resource use and associated costs, subsequent economic modelling showed that TLA would be cost-effective in Sweden at the current monthly rental price (SEK 2,000, ≈ £167), mainly due to increases in quality of life.[33]

Using results from a very small randomized controlled cross-over trial in Sweden, a modelling study addressed the potential cost-effectiveness of TLA therapy over a projected 5-year period.[35] Assuming no impact of TLA on healthcare resource use, TLA was cost-effective when compared to placebo at a device cost of €8,200 (≈£6,890), at a willingness to pay threshold of €35,000 (≈£30,000) per QALY gained. We believe the greatest cost-benefit will occur in severe asthma through reducing exacerbations, which was not addressed in the Swedish trial due to a short observation period.

A further pragmatic, patient-centred RCT of this novel non-pharmacological treatment in severe allergic asthma is now warranted.

7. AIMS AND OBJECTIVES

Our aim is to assess whether home-based nocturnal TLA treatment can effectively reduce asthma related morbidity over a 1-year period in a real-life group of poorly-controlled, severe allergic asthmatic patients.

7.1 Primary Objective

To determine whether nocturnal TLA treatment reduces the frequency of severe asthma exacerbations (defined as an acute deterioration in asthma requiring treatment with systemic corticosteroids).

7.2 Secondary Objectives

- To assess the impact of nocturnal TLA treatment on asthma control which includes:
  - Current clinical asthma control which is the extent to which the clinical manifestations of asthma (symptoms, reliever use, and airway obstruction) have been reduced or removed by treatment.
  - The risk of future adverse asthma outcomes which includes loss of control, exacerbations, accelerated decline in lung function, and side-effects of treatment.
- To ascertain the effect of TLA treatment on quality of life in poorly-controlled severe allergic asthmatic participants and their carers.
- To qualitatively evaluate the perceptions, values and opinions of the device to identify potential modifications to improve patient acceptance and to inform future implementation of the device within the NHS setting.
- To evaluate the impact of TLA treatment on healthcare utilisation and related costs, and its impact on education/work days lost.
- To fully assess the cost-effectiveness, both at one-year and over the lifetime of the patient, of nocturnal TLA treatment using a cost-utility analysis to determine the incremental cost per QALY gained.

7.3 Exploratory Objective

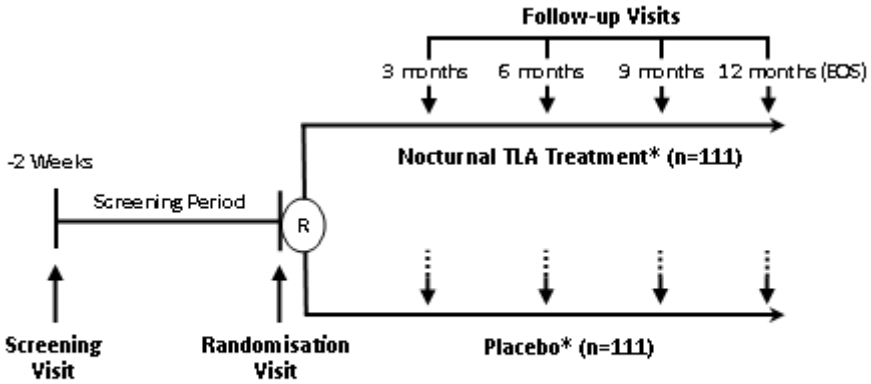
- To assess patient and environmental factors associated with a treatment response

8. STUDY DESIGN

8.1 Summary of Study Design

A multi-centre randomised, double blind, placebo-controlled, parallel group trial of 12-months participant duration with a 4-month internal pilot. Each participant will be required to attend 6 study visits.

Figure 8.1 Study Design



* In addition to existing asthma treatments which will not be adjusted during the trial

R = Randomisation

Further details of the study design are included in the Trial Flowchart (Appendix 2)

8.1.1 Rationale for Placebo as Comparator

A placebo comparator has been chosen as other add-on treatments in severe asthma (e.g. Omalizumab and Bronchial Thermoplasty) vary greatly in indication, use and delivery, are not suitable for every patient, and would therefore not be able to be used consistently or safely in an 'active' control group.

Throughout the trial, participants in both treatment arms will receive standard asthma care in accordance with the national BTS/SIGN guidelines for the management of asthma in adults.

8.1.2 The Internal Pilot

The internal pilot will evaluate trial processes over the first 4-months of recruitment, at the 5 initial recruiting centres, including:

- Recruitment and retention of participants Data collection methods and quality
- Participant and partner experience

8.1.2.1 Recruitment and Retention of Participants

ORTU will summarise the following for review by the TSC:

- Screening and consent logs and number of participants successfully randomised from sites
- Time to device installation from randomisation
- Adherence to follow-up (including 1 month telephone review)

8.1.2.2 Data Collection Methods and Quality

The data manager based at ORTU will complete a review of data quality and completeness including an assessment of exacerbation reporting and the completeness of participant diaries, case report forms and questionnaires for all participants enrolled into the trial.

8.1.2.3 Participant and Partner Experience

Informed consent for participation in the qualitative study during the internal pilot will have been sought at Screening Visit 1. Senior qualitative researchers will conduct interviews by telephone in study month 9 (recruitment month 3) using a semi-structured interview schedule. We will invite 10 trial participants and 10 partners (≥18 years) living within the same home and sharing the same bedroom environment to take part in the qualitative interviews. Participants will be selected to represent the different study sites. The qualitative interviews will focus on the study procedures to elicit aspects of the study that may be improved. We will also gather information about their experience of using the TLA device. The qualitative interviews will help to identify potential barriers to recruitment, treatment adherence and device acceptability. Information gained from the qualitative interviews will be used to inform the 'frequently asked questions' section on the LASER Trial website (www.lasertrial.co.uk).

8.2 Primary and Secondary Outcome Measures

The trial uses validated, standardised primary and secondary outcomes for clinical asthma trials recommended by the American and European Thoracic Societies and endorsed by the COMET initiative.[36] Comparison of data at multiple time-points will assess the magnitude and rate of treatment response and variation in level of control.

8.2.1 Primary Outcome

Severe asthma exacerbations occurring within the 12-month follow-up period.

Severe asthma exacerbations are defined in accordance with ATS/ERS guidelines[36] as a worsening of asthma requiring systemic corticosteroids, ≥30mg prednisolone or equivalent daily (or ≥50% increase in dose if maintenance 30mg prednisolone or above) for 3 or more days. Courses of corticosteroids separated by ≥7 days will be treated as separate severe exacerbations.

8.2.2 Secondary outcomes

8.2.2.1 Asthma Control

Current asthma control at 3, 6, 9, and 12 months:

- Lung function measures
  - *Pre*-bronchodilator FEV_1
  - Mean morning pre-bronchodilator Peak Expiratory Flow Rate over 2-weeks preceding follow-up visits
  - Fractional concentration of exhaled Nitric Oxide (F_ENO)
- ACQ score

- ACD score over 2-weeks preceding follow-up visits
- SNOT-22 score

Risk of future adverse asthma outcomes:

- Severe exacerbations (see 8.2.1)
- Systemic corticosteroid use over the 12 month follow-up period
- *Post*-bronchodilator FEV_1 at 12-months

8.2.2.2 Device Usage Data

- Participant reported device usage at 3, 6, 9 and 12 months
- Engineer reported device usage at 6 and 12 months

8.2.2.3 Health Related Quality of Life at 3, 6, 9 and 12 months

- AQLQ(S) score
- EQ-5D-5L score

8.2.2.4 Adult Carer's Quality of Life at 12 months

- AC-QOL score

8.2.2.5 Global Evaluation of Treatment Effect at 12 months

- GETE score

8.2.2.6 Health Economics

- Healthcare resource use and cost over the 12-month follow-up period
- Informal care required by participants over the 12-month follow-up period
- WPAI(A) at 3, 6, 9 and 12 months to measure the impact of asthma on participants' work/activity productivity
- WPAI(CG) at 12 months to measure the impact of asthma on carers' work/activity productivity

8.2.2.7 Qualitative Outcomes

- Participant and partner's perception of the treatment device

8.2.2.8 Outcomes for Exploratory Analyses

- Factors associated with treatment response including device adherence, objective markers of bronchial and systemic allergy and inflammation, lung function, asthma and rhinitis control, quality of life and indoor air quality.

9. STUDY PARTICIPANTS

9.1 Study Setting

Nocturnal TLA treatment will be provided in the patient's home and research visits will take place at centres with experience of treating severe asthma.

9.2 Target Population

- Adults (16-75 years) with severe, poorly-controlled asthma (as defined by ATS/ERS Guideline 2013[32]) despite high intensity treatment who are sensitised to a perennial indoor aeroallergen (House Dust Mite (HDM), domestic pet or fungi), to which they are likely to be exposed during the study.

In addition, carers and/or partners will be included in the trial according to the following definitions:

- Trial participant's adult carer (≥18yrs) who provides unpaid support to a participant who could not otherwise manage without this help.
- Trial participant's partners (≥18 years) living within the same home and sharing the same bedroom environment.

9.3 Eligibility Criteria

The chosen eligibility criteria closely mirror those of previous studies showing the rates of severe exacerbation used for statistical modelling in this trial (see Appendix 1).

9.3.1 Inclusion Criteria

A potential participant must meet **ALL** of the following inclusion criteria at Randomisation Visit 2 to be considered eligible for the study:

- **Adults** (aged 16-75 years inclusive)
- **A clinical diagnosis of asthma** for ≥6 months supported by evidence of *any one* of the following:
    - Airflow variability with a mean diurnal peak expiratory flow (PEF) variability[i] >15% during the baseline 2-week period or a variability in FEV_1 of >20% across clinic visits within the preceding 12 months, with concomitant evidence of airflow obstruction (FEV_1/FVC ratio <70%);
    - Airway reversibility with an improvement in FEV_1 by ≥12% or 200 ml after inhalation of 400 µg of salbutamol via a metered dose inhaler and spacer at first study visit or within the preceding 12 months;
    - Airway hyper-responsiveness demonstrated by Methacholine challenge testing with a provocative concentration of Methacholine required to cause a 20% reduction in FEV1 (PC_{20}) of ≤8mg/ml or equivalent test (See Appendix 3).
- **Severe asthma**

[i] Mean diurnal peak expiratory flow (PEF) variability calculated by ((PEF[highest]-PEF[lowest]) / (PEF[mean]))

- Requirement for high-dose inhaled corticosteroids (ICS) (≥1000µg/day beclomethasone (BDP) or equivalent – see Appendix 4) plus a second controller (long-acting ß2-agonist or anti-muscarinic, theophylline, or leukotriene antagonist), and/or systemic corticosteroids.
- If on maintenance corticosteroids, the maintenance dose must have been stable for 3-months– this excludes any interim need for short-term steroid bursts to treat exacerbations.

- **Poorly controlled asthma** demonstrated by **BOTH**:
  - ≥2 severe asthma exacerbations, requiring systemic corticosteroids ≥30mg prednisolone or equivalent daily (or ≥50% increase in dose if maintenance 30mg prednisolone or above), for 3 or more days, during the previous 12 months, despite the use of high-dose inhaled corticosteroids (ICS) and additional controller medication;
  - ACQ (7-point) score >1 at Screening Visit 1 and Randomisation Visit 2.
- **Atopic status**
  - Sensitisation to ≥1 perennial indoor aeroallergen[ii] (including House Dust Mite, domestic pet or fungi) to which they are likely to be exposed during the study, demonstrated by a positive skin prick test (wheal diameter ≥3mm more than negative control) or specific IgE ≥0.35 IU/L).
- Exacerbation free and taking stable maintenance asthma medications (not including short-acting bronchodilator or other reliever therapies) for at least 2-weeks prior to Screening Visit 1
- Exacerbation free and taking stable maintenance asthma medications (not including short-acting bronchodilator or other reliever therapies) in the period between Screening Visit 1 and Randomisation Visit 2.(the Screening Period). Participants suffering a severe exacerbation during the Screening Period can be rescreened 2 weeks after returning to their maintenance asthma medications (See 11.3.2)
- Able to use the TLA device during sleep on at least five nights per week (excluding holidays)
- Able to understand and give written informed consent prior to participation in the trial and able to comply with the trial requirements

9.3.2 Exclusion Criteria

A potential participant who meets **ANY** of the following exclusion criteria will be excluded from participating in the study:

- Current smokers or ex-smokers abstinent for <6months
- Ex-smokers with ≥15 pack year smoking history.
- Partner who is a current smoker and smokes within the bedroom where the TLA device is installed
- TLA device cannot be safely installed within the bedroom
- Intending to move out of study area[iii] within the follow-up period
- Documented poor treatment adherence

[ii] Suggested screening panel *Dermatophagoides pteronyssinus* (Der p 1) or *Dermatophagoides farinae* (Der f 1),) *Aspergillus fumigatus* (Asp f 1), *Alternaria alternarta* (Alt a 1) or *Cladosporium herbarum* (Cla h 1), Cat - *Felis domesticus* (Fel d 1), Dog - *Canis familiaris* (Can f 1)

[iii] Participants moving out of the study area after randomisation will not be automatically withdrawn. Every effort will be made to continue treatment and trial follow-up.

- Occupational asthma with continued exposure to known sensitising agents in the workplace
- Previous bronchial thermoplasty within 12 months of randomisation
- Treatment with Omalizumab (anti-IgE) within 120 days of randomisation
- Using long-term oxygen, Continuous Positive Airway Pressure (CPAP) or Non-Invasive Ventilation (NIV) routinely overnight as this will impair the effect of the TLA device
- Uncontrolled symptomatic gastro-oesophageal reflux that may act as a persistent asthma trigger.
- Presence of clinically significant lung disease other than asthma, including smoking-related chronic obstructive pulmonary disease (COPD), bronchiectasis associated with recurrent bacterial infection, allergic bronchopulmonary aspergillosis (mycosis), pulmonary fibrosis, sleep apnoea, pulmonary hypertension, or lung cancer, that in the opinion of the Principal Investigator is likely to be contributing significantly to the participant's symptoms.
- Clinically significant co-morbidity (including cardiovascular, endocrine, metabolic, gastro-intestinal, hepatic, neurological, renal, haematological and malignant conditions) that remains uncontrolled with standard treatment.
- Patients currently taking part in other interventional respiratory clinical trials.

10. SAMPLING

10.1 Sample Size Justification

Based on an estimated rate of 2 severe asthma exacerbations per participant over the 12-month period in the placebo group (see Appendix 1) a minimum of 222 participants (111 per group) will be required to provide 80% power (at 5% two-sided significance level) to detect a clinically meaningful 25% reduction in the average exacerbation rate in the group using the TLA device.

This sample size is based on a Poisson regression model with the treatment group as the covariate and a 10% overall dropout rate.[37] A review of comparative interventions of proven efficacy in severe asthma gave effect sizes ranging from 21% to 63%, mean 41% (see Appendix 1). Given that this is a pragmatic trial where we expect our intervention to be less effective than an efficacy trial, we have chosen a deliberately more conservative effect size of 25%.This represents on average, one less severe exacerbation every two years.

11. STUDY PROCEDURES

11.1 Resources and Equipment Required at Recruitment Sites

- Spirometry equipment conforming to ATS/ERS standards 2005[38].
- Bronchodilator (Salbutamol MDI) medication and spacer device for performing bronchodilator reversibility testing.
- NIOX Mino® (Aerocrine AB, Solna, Sweden) or alternative device for measuring Fractional exhaled Nitric Oxide (F_ENO.)
- Access to skin prick testing for sensitisation to common indoor aero-allergens, Der p 1, Der f 1, Asp f 1, Alt a 1, Cla h 1, Fel d 1 and Can f 1.

- Access to Methacholine challenge testing or alternative broncho-provocation testing.
- Access to laboratory services to measure peripheral blood eosinophil count, serum total IgE and serum specific IgE to Der p 1, Der f 1, Asp f 1, Alt a 1, Cla h 1, Fel d 1 and Can f 1.
- Computer access with Universal Serial Bus (USB) for downloading PEF diaries.

PEF devices, PEF interpretation software, patient diaries and questionnaires will be provided by the sponsor.

11.2 Recruitment

Trial sites will be selected based on robust feasibility assessments demonstrating an ability to recruit participants meeting the eligibility criteria. Some sites will have large cohorts of severe asthma patients with detailed clinical and biological data in preparation for clinical trial inclusion. Participants meeting the eligibility criteria will be recruited from these existing cohorts (prevalent cases) as well as from new referrals to the Severe Asthma Services (incident cases) at participating sites.

Potential participants will be identified via the following methods:

- Cohort databases
- Existing clinic registers
- Referrals to the severe asthma clinics
- Participant self-referral in response to advertisements

Following review of eligibility criteria (including age, smoking status, co-morbidity and severe asthma diagnosis) potential participants will be provided with further information either at an Information Event or by their local research team. Participants identified from existing cohort databases or self-referring will be approached directly by the site research teams. Participants identified from clinic registers and severe asthma clinics will be approached by their clinical team and, if interested, referred to the site research teams.

Participants will be asked to invite their carer and/or partner to attend the Information Event or Screening Visit 1 where appropriate.

11.2.1 Anticipated Recruitment Rates and Recruitment Targets

Study Month	Recruitment Months	Recruitment Rate	Number Recruited	Recruitment Total
7-10	1-4	16/month	64	**64**
11-17	5-11	14/month	98	**162**
18-21	12-15	10/month	40	**202**
22-24	16-18	7/month	20	**222**

Recruitment Targets	
4 Months	64 Participants
11 Months	162 Participants

(Extrapolated recruitment total based on pilot recruitment rate over substantive study = 270)

Study recruitment and progress will be monitored by the HTA adhering to pre-set recruitment milestones.

11.2.2 Information Events

A series of Information Events to cover all sites will be led by the trial teams and patient representatives from the 5 initial participating sites within the first 6 months of trial recruitment. These meetings will include a demonstration of the device and a short presentation by the site trial team. Potential participants will be offered a paper template cut-out to demonstrate whether the device can be fitted

within their bedroom, a participant information sheet (PIS) including contact information for the trial team and a trial leaflet. Potential participants who are unable to attend the information events but would like further information will be sent a DVD of the device demonstration as well as the device template, PIS and trial leaflet.

The local trial team will subsequently contact potential participants and invite those who wish to take part in the study to a Screening Visit.

11.2.3 Trial Advertisements

Ethically approved trial advertisements at General Practices, in Respiratory Outpatient Departments and on the LASER Trial website (www.lasertrial.co.uk) will be used to raise awareness of the trial. Contact details of the trial team will be displayed for patients interested in taking part in the trial.

11.3 Screening and Enrolment

11.3.1 Screening Visit 1 (-2 weeks)

- Informed Consent will be sought for participation in the main trial as well as the qualitative studies (see 8.1.2.3 and 11.7.10) at Screening Visit 1. Informed Consent will precede any study procedures (including tests to ascertain eligibility for trial inclusion) ensuring the participant has had an opportunity to fully discuss the PIS with the research team.
- Further evaluation of inclusion and exclusion criteria to determine eligibility will include:
  - Baseline spirometry including reversibility testing
  - Skin Prick Testing to Der p 1, Der f 1, Asp f 1, Alt a 1, Cla h 1, Fel d 1 and Can f 1. (can be delayed to Randomisation Visit 2 if necessary)
  - Blood tests (peripheral eosinophil count, total serum IgE in all cases and specific serum IgE testing if SPT not available)
  - ACQ score
- Issue and record participant training in use of electronic PEF meter to measure morning and evening PEF (instruct participants to measure morning and evening PEF before taking asthma medications) for 2-weeks prior to Randomisation Visit 2
- Issue and record participant training in use of Asthma Control Diary to be completed for 2-weeks prior to Randomisation Visit 2
- If not already provided and appropriate give participant a PIS for their adult carer and/or partner should they wish to participate.

11.3.2 Extension of Screening Period

Participants must demonstrate acceptable compliance with the electronic PEF recordings and Asthma Control Diary during the 2-week screening period. However, in the event the electronic PEF device malfunction or, if in the investigator's opinion, there are significant extenuating circumstances the screening period may be extended by up to a further 2-weeks. Participants experiencing a severe exacerbation during the screening period will no longer be eligible but can be re-screened 2-weeks after returning to their maintenance asthma medications.

11.3.3 Randomisation Visit 2 (0 Months)

Data collected during the screening period and Randomisation Visit 2 will be used both to assess whether the participant fulfils additional eligibility criteria and also as baseline data to be included within the CRF.

- Demographics, asthma history and asthma review (see below)
- Review of electronic PEF diary
- Review of Asthma Control diary
- ACQ score

Participant eligibility can now be confirmed and participant randomised (see 11.4)

- SNOT-22, AQLQ(S), EQ-5D-5L, WPAI(A) and Indoor Air Quality questionnaires
- Fractional concentration of exhaled nitric oxide (F_ENO)
- Baseline spirometry after withholding bronchodilator (Pre-bronchodilator FEV_1)
- Calculate participants 'exacerbation-dose' of systemic corticosteroids (see 11.6.1.2) and issue at least 3 Exacerbation Diaries.
- Issue LASER diary for self-reported device usage and healthcare utilisation throughout the follow-up period.
- Issue 2-week Asthma Control Diary (including electronic PEF recordings) for completion prior to 3 month follow-up visit.
- If appropriate seek informed consent from participant's carer (if participant's carer is unable to attend, an additional appointment should be arranged). After giving informed consent carer completes:
  - AC-QOL questionnaire
  - WPAI(CG) questionnaire
- If appropriate seek informed consent from participant's partner for inclusion in the qualitative study (if participant's partner is unable to attend, an additional appointment should be arranged).

11.4 Randomisation

Provided participants fulfill all the eligibility criteria at Randomisation Visit 2 the trial team at the recruiting site will contact ORTU to arrange randomisation. Participants will be randomised in a 1:1 ratio to receive either an active TLA device, or a placebo device. Randomisation will be undertaken centrally by Sealed Envelope™ using a validated computer randomisation program including a nondeterministic minimisation algorithm to ensure treatment concealment and balanced allocation of participants across the two treatment groups for clinical site, prevalent vs. incident cases and the following prognostic factors at baseline: exacerbation frequency in the previous 12 months (2, 3, ≥3), use of oral corticosteroids (yes/no) and pre-bronchodilator FEV1 (>50% predicted yes/no.) as these are key indicators of future exacerbation risk.

11.5 Device Installation

Once eligibility and consent has been confirmed, the local trial team will contact ORTU with the participant's details (Name, Study Number, Address and Contact Telephone Number) and minimisation details. The local trial team will inform the participant that they will be contacted by an engineer within

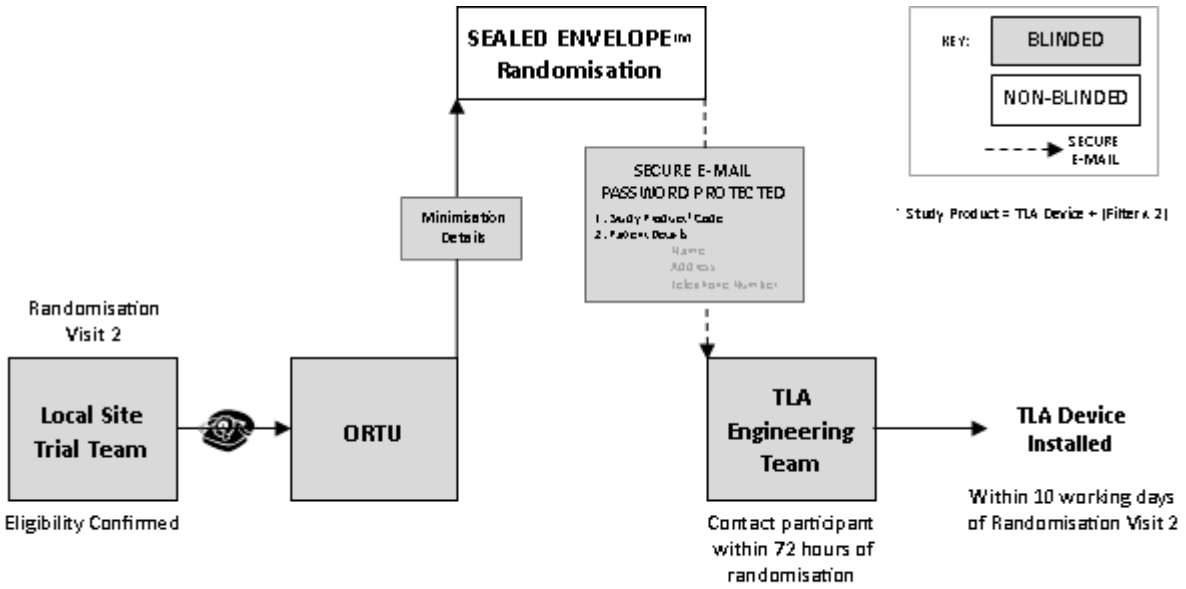
72hrs to arrange device delivery and installation. Delivery and installation will occur within 10 working days of Randomisation Visit 2.

ORTU will randomise the patient using Sealed Envelope™. Sealed Envelope™ will have been provided with a list of TLA product* serial numbers by the manufacturing team based in Sweden and will allocate a specific TLA product to the participant. A secure e-mail notification will be sent immediately to the local trial team to confirm randomisation and secure e-mail and SMS will be sent to the UK based engineering team. This will include the participant's trial number, TLA product serial number and an exclusive link for the engineering team to log in and access the patient's contact details.

The engineering team will then contact the participant (within 72hrs of Randomisation Visit 2) to arrange device delivery and installation following the Device Installation TSP.

** A 'TLA product' consists of a TLA device (active or placebo) plus 2 corresponding TLA device filters. Each TLA product will have a unique serial number.*

Figure 11.5.1 Device Installation



11.6 Double-Blind Treatment Phase

11.6.1 Severe Asthma Exacerbation Reporting

11.6.1.1 Definition of Severe Asthma Exacerbation

Severe asthma exacerbations will be defined according to guidelines from American Thoracic Society/European Respiratory Society[36] as a worsening of asthma requiring systemic corticosteroids ≥30mg prednisolone or equivalent daily (or ≥50% increase in dose if maintenance 30mg prednisolone or above), for 3 or more days. Courses of corticosteroids separated by ≥7 days will be treated as separate severe exacerbations.

Based on this an 'exacerbation-dose' of systemic corticosteroids is defined as ≥30mg prednisolone or equivalent daily if not on maintenance systemic corticosteroid treatment or ≥50% increase in dose if maintenance 30mg prednisolone or above).

11.6.1.2 Exacerbation Reporting

Participants will start an Exacerbation Diary when starting an 'exacerbation-dose' of systemic corticosteroids (participant specific 'exacerbation-dose' is defined at Randomisation Visit 2). The Exacerbation Diary will include PEF measurements (using the trial electronic PEF device), oral corticosteroid dose, reliever medication use and nocturnal asthma symptoms. Participants will be asked to report severe exacerbations to their local site trial team as soon as possible after onset. A dedicated LASER trial mobile telephone at each site will allow direct contact within working hours and out-of-hours a voicemail or text message can be left which the local trial team will respond to at the earliest opportunity. A secure NHS e-mail account will also be available to contact the local trial team if preferred by participants.

Wherever possible, participants will be asked to attend an exacerbation review with their local trial team within 72 hours to corroborate a severe asthma exacerbation. Participants are asked to complete the Exacerbation Diary until this review. At the exacerbation review the local trial team will complete the Exacerbation Visit CRF using the Exacerbation Diary. To corroborate the diagnosis of a severe exacerbation the participant must fulfil the definition of a severe asthma exacerbation with *any one* of the following additional criteria:

- An associated decrease in morning PEF compared to maximum morning PEF achieved at baseline
- A 50% increase in reliever medication on at least 2 of 3 successive days compared to baseline
- Increased nocturnal wakening

Participants are encouraged to attend for an exacerbation review, but where this is not possible the participant should still complete the Exacerbation Diary which will be collected at the next follow-up visit.

Following an exacerbation visit the participant will record usage of 'exacerbation-dose' systemic corticosteroids on the TLA diary until systemic corticosteroids are stopped or dose is reduced to their baseline.

Participants will have LASER 'identity cards' identifying their participation in the trial to their medical team should they require urgent unscheduled healthcare. This will also contain the contact number for the LASER trial mobile telephone at their local site and the secure NHS e-mail address. These details will also be available on the LASER Trial website.

11.6.1.3 Asthma Exacerbations Coinciding with Follow-up Visits

Participants who suffer a severe exacerbation of their asthma or are taking 'exacerbation-dose' systemic corticosteroids within 2-weeks of a follow-up visit will be asked to complete all study procedures for the follow-up visit. This includes the 2-week Asthma Control Diary and lung function measures provided the participant is able to do so and in the PIs clinical judgement this will not cause deterioration in their clinical condition. It will be recorded in the CRF that the participant was in an 'exacerbation state'.

11.6.2 Post-Randomisation Telephone Review (1 Month +/- 3 days)

Participants will be contacted after 1 month (+/- 3 days) to discuss device usage and ensure any technical device issues have been addressed.

11.6.3 Follow-up Visits (3, 6, 9 and 12 month +/- 1 week)

At the 3, 6, 9 and 12 month (+/- 1 week) follow–up visits, measures of current clinical asthma control and the risk of future adverse asthma outcomes will be recorded by means of a combination of questionnaire tools, symptom diaries and lung function measurements. Participants will also be asked to report device adherence, healthcare usage and work/study days lost due to asthma symptoms with the help of their LASER diary and Resource Use Log. At their final follow-up visit participants will be offered the option of the Post-Trial Provision Period (see 11.6.4).

11.6.4 The Post-Trial Provision Period

All participants completing 6-months of the follow-up period will be eligible for treatment with an active TLA device, free of charge including filters and technical support, for a 4-year period (the Post-Trial Provision Period) which will commence no earlier than 12-months post-randomisation. Participants will not be able to find out whether they had an active or placebo device during the trial.

11.7 Study Assessments

11.7.1 Demographics, Asthma History and Asthma Reviews

11.7.1.1 Demographics

- Age
- Gender
- Socio-economic class
- Ethnicity

11.7.1.2 Asthma History

- Date of asthma diagnosis
- History of life threatening and near fatal asthma exacerbations (ITU admissions)
- Number of severe asthma exacerbations in previous 12 months
- History of previous asthma treatments
- History of atopy
- Family history of asthma/atopy
- Asthma triggers
- Medical or surgical co-morbidities
- Occupational history
- Smoking history
- Height / Weight for measuring predicted lung function

  Height (cm) and weight (kg) measured to the nearest 0.1kg

11.7.1.3 Asthma Review

- History of severe asthma exacerbations since previous trial visit and current patient-reported clinical status (still in exacerbation or recovered)
- Current asthma symptoms and treatment
- Current medications
- Additional asthma review questions for Follow-up Visits only:
  - Unscheduled asthma related healthcare use
  - Work / study days lost as a result of asthma symptoms

11.7.2 Lung function measures

11.7.2.1 Pre-bronchodilator FEV1

Spirometry will be conducted using a spirometer conforming to ATS/ERS standards[38] as specified by the manufacturer's instructions. FEV_1 (L), FVC (L), FEV_1/FVC ratio and FEF_{25-75} (%). FEV_1 and FVC will be documented as both absolute values and as a percentage of the predicted value. Measurements will be made at Screening Visit 1, Randomisation Visit 2 and at the 3, 6, 9 and 12 month visits.

11.7.2.2 Reversibility Testing

Post bronchodilator FEV_1 will be measured at Screening Visit 1 and at the 12 month follow up visit. Following ATS/ERS standards,[38] post-bronchodilator FEV_1 will be defined as FEV_1 recorded 15 minutes after administration of 400µg Salbutamol via a metered dose inhaler and spacer device. An improvement in FEV_1 post bronchodilator of ≥12% or 200mls will be considered significant. Both percentage change and volume change will be documented.

11.7.2.3 Fractional concentration of exhaled nitric oxide (F_ENO)

F_ENO will be measured using a NIOX MINO® device (Aerocrine AB®, Solna, Sweden) as specified by the manufacturer's instructions and outlined in the ATS/ERS standards.[39] Measurements will be made before spirometry is performed at Randomisation Visit 2 and at the 3, 6, 9 and 12 month follow up visits.

11.7.3 Allergy Testing

11.7.3.1 Skin Prick Testing

A standard skin prick test procedure using common indoor aeroallergen (Der p 1, Der f 1, Asp f 1, Alt a 1, Cla h 1, Fel d 1 and Can f 1) extracts along with negative (saline) and positive (histamine) controls will be performed on all subjects at Screening Visit 1 (Randomisation Visit 2 if antihistamine hold required. See Appendix 5.) Skin prick testing will be performed in accordance with the Practice Parameter released by the American Academy of Allergy, Asthma and Immunology.[40] A positive skin prick test reaction will be measured as a wheal of at least 3mm in diameter greater than the negative control.

11.7.3.2 Serum Specific IgE Testing

If skin prick testing is not available, a blood sample will be taken at Screening Visit 1 to measure serum specific IgE to common indoor aeroallergens (Der p 1, Der f 1, Asp f 1, Alt a 1, Cla h 1, Fel d 1 and Can f 1.) A specific serum IgE >0.35IU/L will be considered to represent allergen sensitisation. Serum specific IgE testing may also be used if there is uncertainty about a skin prick test result or there is a negative skin prick test result in the context of a patient on long term maintenance systemic corticosteroids.

11.7.3.3 Measurement of Serum Total IgE and Peripheral Blood Eosinophil Count.

A blood sample will be collected at Screening Visit 1 to measure serum total IgE and peripheral blood eosinophil levels.

11.7.4 Participant Questionnaires

11.7.4.1 Asthma Control Questionnaire (ACQ.)

This well validated 7 item questionnaire will be used to assess asthma control over the previous 7 days. The Asthma Control Questionnaire (ACQ)[41] includes 5 symptom scores, the amount of daily rescue bronchodilator use and a measure of airway calibre (FEV1% predicted.) Responses are given on a 6 point scale and the overall score is the mean of the responses (0=totally controlled, 6=severely uncontrolled). The ACQ has strong evaluative and discriminative properties and has been shown to be very responsive to within-patient changes in asthma control over time. The ACQ has a validated minimal important difference of 0.5 to demonstrate clinical significance. The ACQ will be administered at the same time during each visit with the participant blind to the results of other tests. Results will be recorded at Screening Visit 1, Randomisation Visit 2 and at the 3, 6, 9 and 12 month visits.

11.7.4.2 Standardised Asthma Quality of Life Questionnaire (AQLQ(S))

Asthma-specific quality of life will be measured using the Standardised Asthma Quality of Life Questionnaire (AQLQ(S))[42] The AQLQ(S) consists of 32 questions within 4 domains (symptoms, activity limitation, emotional function and environmental stimuli) and has strong measurement properties and a validated minimal important difference of 0.5.[43] Patients are asked to think about how they have been during the previous two weeks and to respond to each of the 32 questions on a 7-point scale (7 = not impaired at all, 1 = severely impaired). The overall AQLQ score is the mean of all 32 responses and the individual domain scores are the means of the items in those domains. The AQLQ score will be recorded at Randomisation Visit 2 and at the 3, 6, 9 and 12 month visits.

11.7.4.3 EuroQol-5 Dimensions 5-levels (EQ-5D-5L.)

Generic Health-Related Quality of Life (HRQoL) will be measured using the EuroQol-5 Dimensions 5-levels (EQ-5D-5L) questionnaire.[44] The EQ-5D-5L is a standardised measure of health providing a simple generic measure of health for clinical and economic appraisal. EQ-5D-5L is the most widely used HRQoL measure in adults in the UK. The EQ-5D-5L has been shown to be a reliable and valid means of measuring QoL in asthma patients[45] The EQ-5D-5L score will be recorded at Randomisation Visit 2 and at the 3, 6, 9 and 12 month visits.

11.7.4.4 22-item Sino-Nasal Outcome Test (SNOT-22.)

The 22-item Sino Nasal Outcome Test (SNOT-22) score is a well validated and sensitive measure of

rhinosinusitis health status.[46]. The SNOT-22 questionnaire consists of 22 questions related to symptoms and the social/emotional impact of those symptoms (rating symptoms on a scale from 'no problem'/0 to 'problem as bad as it can be'/5.) Patients are asked to rate the problems as they have been during the previous 2 weeks. The SNOT-22 score will be recorded at Randomisation Visit 2 and at the 3, 6, 9 and 12 month visits.

11.7.4.5 Indoor Air Quality Questionnaire

The Indoor Air Quality Questionnaire is a bespoke domestic indoor air quality assessment tool derived from a combination of the Stockholm and Southampton Indoor Environment Questionnaires. It will identify key factors affecting air quality within the home environment. This will be completed by participants at Randomisation Visit 2.

11.7.4.6 Global Evaluation of Treatment Effect (GETE.)

The Global Evaluation of Treatment Effect (GETE) questionnaire[47] is a simple measure of perceived treatment effectiveness that has been used in the evaluation of other treatments in patients with severe allergic (IgE mediated) asthma. At the end of the study, at the 12 month visit, participants and physicians will be asked to rate the global treatment effectiveness of the TLA device as excellent (complete control of asthma), good (marked improvement of asthma), moderate (discernible but limited improvement in asthma), poor (no appreciable change in asthma), or worsening (deterioration in asthma.)

11.7.4.7 Work Productivity and Activity Impairment (WPAI(A))

The WPAI(A) is a validated questionnaire tool comprising 6 questions addressing absenteeism, presenteeism (reduced effectiveness whilst working,) overall work productivity loss (absenteeism + presenteeism) and activity impairment.[48] Participants will be asked to recall events over the previous 7 days. WPAI(A) outcomes are measured as percentages and a higher percentage relates to greater impairment and reduced productivity. A modified WPAI(A) will be used for student participants. The WPAI(A) will be completed at Randomisation Visit 2 and at the 3, 6, 9 and 12 month visits by participants.

11.7.5 Adult Carer Questionnaires

11.7.5.1 Adult Carer Quality of Life (AC-QoL.)

The Adult Carer Quality of Life questionnaire is a 40 item questionnaire that measures the overall quality of life of adult, unpaid carers in 8 domain subscales. The 8 domains are support for caring, carer choice, carer stress, money matters, personal growth, sense of value, ability to care and carer satisfaction. Carers are asked to recall experience over the previous 2 week period. Scores on the questionnaire have a possible range of 0-120 with higher scores indicating better carer quality of life. Carers will be asked to complete the AC-QoL at Randomisation Visit 2 and again at the 12 month visit.

11.7.5.2 Work Productivity and Activity Impairment (WPAI(CG))

A modified WPAI (see 11.7.4.7) for care-givers (WPAI(CG)) will be completed at Randomisation Visit 2 and at the 12 month visit.

11.7.6 Pre-Visit Data Collection

11.7.6.1 Asthma Control Diary

At Screening Visit 1, Randomisation Visit 2 and at the 3, 6 and 9 month visits, participants will be issued with an Asthma Control Diary to record data for 2 weeks leading up to Randomisation Visit 2 and the 3, 6, 9 and 12 month visits.

Participants will record the following data on a daily basis for 2 weeks:

Peak Expiratory Flow (PEF) Rate

Participants will perform 3 morning PEF measurements using a hand-held device to be supplied by the trial team. During the screening period participants will also perform 3 evening PEF measurements to assess variability as part of eligibility assessment. This additional PEF data will be stored on the PEF device and downloaded at Randomisation Visit 2.

Symptom and Reliever Medication Use Diary

Participants will document their daily symptom scores using the validated Asthma Control Diary.[49] The Asthma Control Diary measures a morning score (2 items; 0-6 point scale,) a bedtime score including bronchodilator requirement (4 items; 0-6 point scale.) and a best morning peak expiratory flow rate measured as percentage of predicted best (0-6 point scale.) The overall daily score is the mean of the responses (0=perfectly controlled, 6=severely uncontrolled.)

11.7.6.2 Device Usage Data (follow-up visits only)

Device usage data (displayed on the device screen) documenting the number of hours device active will be collected by:

- Participants at 3, 6, 9 and 12 months to coincide with follow-up visits
- Engineering team at 6 and 12 months to coincide with planned filter changes.

11.7.7 LASER Diary

Participants will be issued with a LASER diary at Randomisation Visit 2. Participants will record whether they used the TLA device on a daily basis. This will be used as a measure of patient reported treatment adherence.

The LASER diary will also be used by participants to record healthcare usage, work/study days lost through asthma symptoms and whether they are taking oral corticosteroids for an asthma exacerbation.

11.7.8 Resource Use Log

Participants will be issued with a resource use log at Randomisation Visit 2 and at the 3, 6 and 9 month visits where they will be able to record healthcare resource use during the 3 month period between study visits to aid recollection of events when asked to recall healthcare use at each follow up visit.

11.7.9 Measurement of Costs and Outcomes to Estimate Cost-Effectiveness

11.7.9.1 Quality Adjusted Life-Years (QALYs)

EQ-5D-5L will be recorded at Randomisation Visit 2 and at the 3, 6, 9, and 12 month follow-up visits. Responses will be converted into utilities using tariffs estimated from a representative sample of the UK population.[50]

Survival information collected from the trial will be combined with EQ-5D utilities to generate Quality Adjusted Life-Years (QALYs.)

11.7.9.2 Healthcare Resource Use and Cost

The perspective adopted in the economic analysis will be that of the National Health Service (NHS). For this perspective we will include the costs associated with the following healthcare resource categories over the 12-month follow-up period:

- Nocturnal TLA device, which includes acquisition, installation, servicing and costs of new filters;
- Prescribed medications for the treatment of asthma;
- Inhaled and oral corticosteroids;
- Primary care contacts, including surgery and home visits by GPs, nurses, and out-of-hours medical services; and
- Hospital care services, including scheduled and unscheduled inpatient admissions, accident and emergency visits and outpatient care contacts.

Primary and hospital care resource use will be obtained from a number of different sources including: patient diaries; review of primary care medical notes; review of patient discharge letters; and Hospital Episode Statistics (HES) records pertaining to any contact in the participating NHS Trusts. Participants will record healthcare resource usage on their LASER diary. Healthcare resources will be valued using unit cost schedules such as PSSRU[51], and NHS Reference costs[52]. Medication costs will be calculated using British National Formulary (BNF) pricing[53]. Information on the acquisition costs of the TLA device and any servicing costs will be obtained from the manufacturer and from information collected as part of the trial. For the within-trial analysis, we will annuitize the costs of the device, with the cost of the device being spread over the device's predicted lifetime and depreciated using equivalent annual costing, discounted at 3.5%[54].

11.7.9.3 Wider economic costs

Through questionnaires, participants will be asked about their use of over-the counter medication and whether they required any informal care (e.g. spouse taking time-off work to care for participant). Hours of informal care will be valued using gender-specific mean wages. For any care-givers not in employment, minimum wages will be used to value such care.

Using the WPAI(A), we will measure, over the 12-month follow-up duration, the number of work/education days lost by study participants and the impact of asthma on their level of productivity/activity. The WPAI(CG) will also be used to assess the impact of caring for an asthma patient on productivity/activity levels.

11.7.10 Qualitative data collection

11.7.10.1 Sampling and Recruitment

Informed consent for participation in the qualitative study will be sought at Screening Visit 1 (see 11.3.1). All participants taking part in the LASER trial will be invited to take part in the qualitative study although this is not mandatory. Participants will be contacted towards the end of their 12 month follow-up period with an invitation to their local focus group interview.

Not all participants who consent to taking part in the focus group interview will be selected. A purposive sampling framework will be used to select participants. 5-10 participants will be selected for each of the focus group interviews on the basis that they best reflect multiple variation (including balance of gender, age and ethnicity.)

11.7.10.2 Focus Groups

Using focus group interviews we will collect qualitative data to capture individual's perceptions, expectations and meaning to explore acceptance, level of personal control, motivation and usefulness of the TLA device. Data will be collected through focus group interviews (two focus group interviews at each of four representative recruitment centres - one of satisfied participants and one of non-satisfied participants at each site.) Two further focus groups will be held to explore the experiences of participant's partners.

Groups of satisfied and non-satisfied participants will be identified from device usage data taken from a combination of device reported usage and patient reported device usage.

A topic guide will be developed using key themes identified during the qualitative telephone interviews conducted during the pilot phase. Free discussion of experiences and ideas will also be encouraged.

Non-NHS (locally accessible) venues will be used for the focus group interviews. Interviews will be digitally recorded, with participant's permission, so that the analysis is based on the full focus group dialogue.

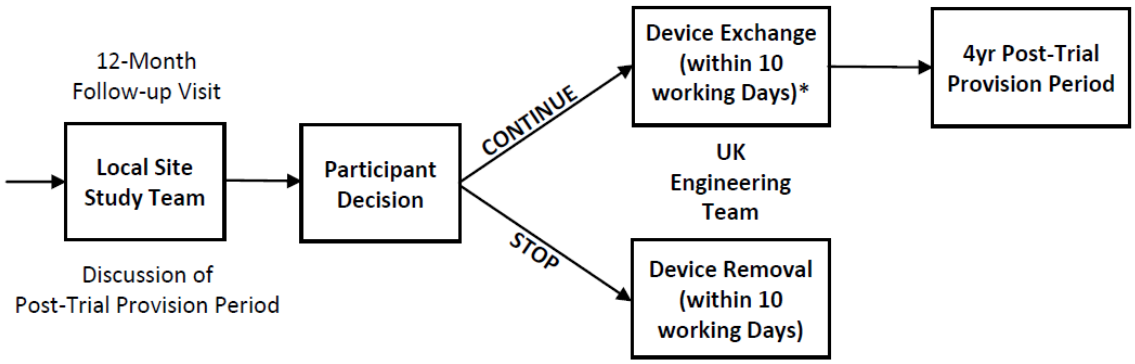
11.8 Device Exchange / Removal

Participants who do not wish to continue with the TLA treatment in the Post-Trial Provision Period will have the device removed from their home within 10 working days.

Participants wishing to take up the Post-Trial Provision Period will be visited by the engineering team. A strict Device Exchange TSP will be followed to preserve patient blinding. All study devices will be removed from the participant's home and active TLA devices will be installed (this may be the same device as used during the follow-up period).

Participants taking part in the qualitative study will have their device exchange delayed until after their focus group interview has taken place.

Figure 11.8 Device Exchange / Removal



* Only after participation in qualitative focus group (if applicable)

11.9 Discontinuation/Withdrawal of Participants from Study Treatment

Participants will be free to withdraw from the trial at any time without having to give a reason. Withdrawal will not affect participant's future care.

Participants withdrawing from the trial will be asked to attend their next scheduled follow-up visit which will complete their trial follow-up. Usual asthma care will continue throughout the follow-up period and following completion of trial participation.

Participants may be withdrawn from the study in the event of any of the following reasons:

- Lost to follow-up. Every reasonable effort will be made to contact the participant and to determine reason for discontinuation or withdrawal.
- Participant re-location. If a patient re-locates and is unable to attend further follow-up visits then they will be withdrawn from the trial.
- Withdrawal of Consent. In the event of a patient withdrawing consent, the reason for withdrawal, if given, will be documented in the CRF and in the source document.
- Serious Adverse Events (SAEs.) Participants may be withdrawn from the study if there is concern about participant's safety related to their ongoing participation in the trial.
- Non-adherence with trial procedures. Participants may be withdrawn from the study if there is concern about persistent or recurrent non-adherence with trial procedures.

11.10 Definition of End of Study

The end of study is the date of the last follow-up visit (12month visit) of the last participant OR the date of the last qualitative focus group meeting, whichever comes last.

12. INTERVENTION

12.1 Description of Study intervention

12.1.1 Active Devices

The active TLA device (Airsonett®) significantly reduces nocturnal allergen exposure by filtering ambient air through a high efficiency particulate air filter, slightly cooling (0·5-0·8ºC) and 'showering' it over the participant during sleep. The reduced temperature allows the filtered air to descend in a laminar stream, displacing allergen rich air from the breathing zone reducing allergen exposure without creating draft or dehydration.[55] The device is installed next to the participant's bed and is easy to use with no identified safety concerns in previous trials. The device is CE marked and licensed for use in the UK for allergic asthma. The device uses the same amount of electricity as a 60W light bulb and has an anticipated life-span of 5 years with filter changes required every 6 months.

12.1.2 Placebo Devices

The placebo devices are adjusted to deliver isothermal air, instead of slightly cooled air, and holes in the filter effectively bypass it whilst still maintaining an equivalent sound and airflow level to an active device. This allows the placebo device to deliver a laminar flow of non-filtered, non-descending, isothermal air which, when mixed with the warm body convection, will ascend towards the ceiling and thus have no effect on the normal air flow pattern around the breathing zone. There is no difference in the air delivery rate, perceived air movements or sound level between an active or placebo device. The human body is not able to detect an absolute temperature difference of 0.75°C and as such there is no perceptible temperature difference sleeping beneath an active or a placebo device. Electricity usage is the same as for active devices and the filter is changed at 6 month intervals.

12.1.3 Validation of Device Function

Prior to shipping, the manufacturer (Airsonett®) will ensure all devices are quality checked to CE standard as well as for air temperature regulation, airflow and breathing zone particle reduction with provision of quality control documentation.

12.2 Adherence to Study Treatment

Study devices will be programmed at installation to automatically turn on for a minimum of 10 hours to cover the participants' normal sleeping hours. This can be overridden by the participant should they wish to start the treatment at a different time or turn off the device. Participants are allowed to increase their usage of the device (e.g. daytime naps) and this will also be documented in the LASER diary.

Participants will document device use on the LASER diary (see 11.7.7) and device usage data (displayed on the device screen) will be collected at follow-up visits (see 11.7.6.3).

12.3 Accountability of the Study Treatment

The device manufacturer (Airsonett®.) will keep a log of serial numbers of all active and placebo study devices and filters. This log will be shared with Sealed Envelope™.

12.4 Standard Asthma Care During the Trial

12.4.1 Treatments when Stable

All participants will have been evaluated by clinicians with expertise in severe asthma, and thus alternative or co-morbid pathologies contributing to poor asthma control will have been excluded and treatment adherence confirmed.

No adjustment or reduction of asthma medications (excluding antihistamines and nasal corticosteroids) will be allowed during the trial (unless required for patient safety reasons) due to the significant risk of precipitating severe asthma exacerbations. Any variation in non-asthma medication usage will be recorded at each follow-up visit (including the use of over the counter medications).

Those participants using variable "Maintenance ± Adjustable Reliever (MART)" therapy that combines inhaled corticosteroid (ICS) and bronchodilator therapy in a single inhaler will be assessed for a threshold ICS dose at Screening Visit 1 (to meet eligibility criteria), and converted to a fixed dose regimen (preferably without changing inhalers) for the duration of the trial and an alternative short-acting bronchodilator (e.g. Salbutamol, Terbutaline) will be provided by the site team.

Participants using Self-Management Plans (SMPs) prior to the trial will be allowed to continue and asked not to change this during the trial treatment period.

12.4.2 Asthma Exacerbations

Asthma exacerbations will be managed following best clinical practice in the appropriate setting following the national BTS/SIGN guidelines.[16]

If participants require urgent medical attention at any time during the follow-up period, they should call 999 and/or attend the Emergency Department. If the participant does not require urgent medical attention, within working hours they should follow their normal process for seeking medical attention either from their GP, practice nurse or asthma specialist. Out of hours they should contact their local primary care out-of-hours service.

Participants who self-manage their oral corticosteroids should contact 999 if they require urgent medical attention or self-manage in the community as directed by their agreed self-management plan if they do not require urgent medical attention.

Participants will report severe exacerbations to their local site trial team as soon as possible after exacerbation onset (see 11.6.1.2.)

Following an exacerbation, corticosteroid treatment should be stopped or reduced to normal maintenance dose as directed by individual patient need.

13. ASSESSMENT OF SAFETY

13.1 Definitions

13.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a participant taking part in a clinical trial which does not necessarily have to have a causal relationship with the device under investigation.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of the device, whether or not this has a causal relationship with the device under investigation.

13.1.2 Adverse Device Effect (ADE)

Adverse Device Effects (ADEs) are all untoward and unintended medical occurrences in response to a medical device.

All cases judged by either a medically qualified professional or the sponsor as having a reasonable suspected causal relationship to the device qualify as a device effect.

This also includes any event resulting from insufficiencies or inadequacies in the instruction for use or deployment of the device and includes any event that is a result of a user error.

13.1.3 Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence that:

- Results in death
- Is life-threatening

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

- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Results in other important medical events

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

To ensure no confusion or misunderstanding of the difference between the terms 'serious' and 'severe', which are not synonymous, the following note of clarification is provided:

- The term 'severe' is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache).

- This is not the same as 'serious,' which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

13.1.4 Serious Adverse Device Effects (SADE)

A SADE is any untoward medical occurrence seen in a patient that can be attributed wholly or partly to the device which resulted in any of the characteristics or lead to the characteristics of a Serious Adverse Event.

A SADE is also any event that may have led to these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune. A SADE will be documented on an SAE form.

13.1.5 Unanticipated Adverse Device Effect (UADE)

An UADE is any Serious Adverse Device Effect that has not previously been identified in nature, severity or degree of incidence in the investigational plan or application (including a supplementary plan or application).

Based on the risk assessment, all SADEs are unanticipated so are also UADEs.

13.2 Safety Monitoring

ORTU will monitor safety in compliance with OCTRU's safety reporting SOP with oversight from the Sponsor.

Based on a risk assessment by the Sponsor, including the following:

- The safety and risk-benefit profiles of TLA treatment
- The well established and expected clinically significant events for severe asthma
- The study endpoints

It has been decided that certain adverse events (see section 3.2.1.2), may be excluded from recording, and subsequent safety analysis, as they do not materially affect participant safety.

Only AEs that have a reasonable possibility of being attributable to the Device (that is an Adverse Device Effect) and any other AE considered to be of clinical significance by the local PI as causing harm to the patient will be recorded in the CRF

13.2.1 Recording Adverse Events

Participants will be asked about the occurrence of any AEs at each follow-up visit and will be asked to report AEs to their local trial team between visits.

AEs will be managed in accordance with the flow chart below (Figure 13.2.1).

AEs will be assessed by the local PI for causality, intensity, seriousness and expectedness.

13.2.1.1 Definition of Causality

The relationship between an adverse event and the study device will be assessed and categorised as below. The assessment will be based upon the PIs clinical judgement to determine the relationship, considering alternative causes, such as natural history of the disease process, concomitant therapy and other risk factors.

The PI should consult the protocol before making a final judgement that the event is one of the following:

- Not related: Temporal relationship of the onset of the event, relative to commencing TLA treatment, is not reasonable or another cause can by itself explain the occurrence of the event
- Unlikely to be related: Temporal relationship of the onset of the event, relative to commencing TLA treatment, is likely to have another cause which can by itself explain the occurrence of the event
- Possibly related: Temporal relationship of the onset of the event, relative to commencing TLA treatment, is reasonable but the event could have been due to another, equally likely cause.
- Probably related: Temporal relationship of the onset of the event, relative to commencing TLA treatment, is reasonable and the event is more likely explained by the product/procedure than any other cause.
- Definitely related: Temporal relationship of the onset of the event, relative to commencing TLA treatment, is reasonable and there is no other cause to explain the event, or a re-challenge (if feasible) is positive.

Where an event is assessed as possibly, probably, or definitely related, the event is an adverse device effect.

13.2.1.2 Expected Adverse Events Exempt from Recording

Participants may experience a number of serious and non-serious adverse events if their asthma control worsens or they suffer a severe exacerbation during the study period. These include:

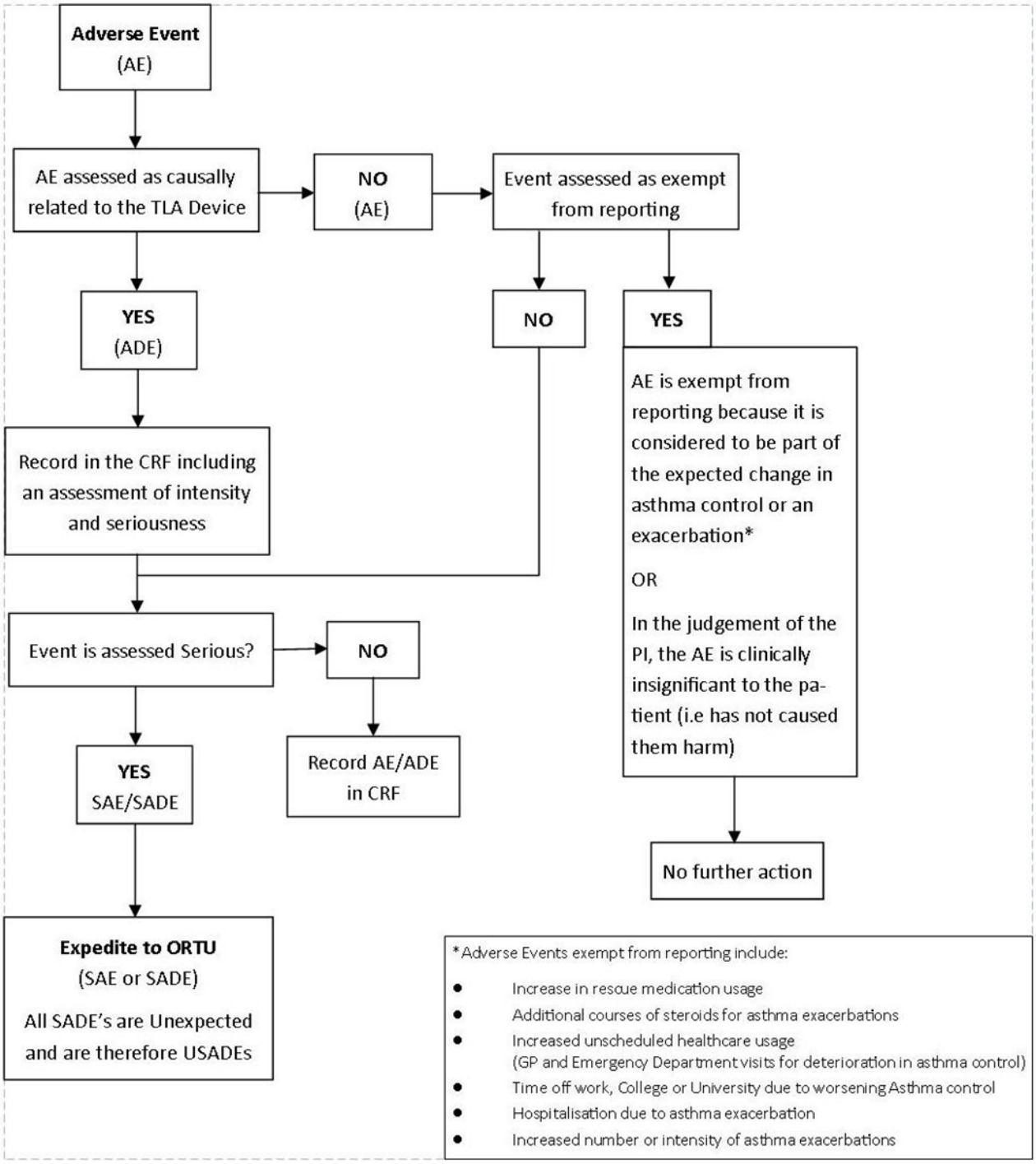
- An increase in rescue medication usage
- Additional courses of steroids for asthma exacerbations
- Increased unscheduled healthcare usage including GP and Emergency Department visits for deteriorations in asthma control
- Time off work, College or University due to worsening Asthma control
- Hospitalisation due to asthma exacerbation
- Increased number or intensity of asthma exacerbations

13.2.2 Recording and Reporting Serious Adverse Events

All SAE/SADEs will be recorded on a Serious Adverse Event Form and expedited to ORTU. All SAE/SADEs will be reported within 24 hours of awareness to ORTU by the PI/delegate at the recruiting centres including a causality assessment. ORTU will perform a second medical assessment of all reported SAE/SADEs and if considered by either the PI or ORTU to be possibly, probably or definitely related to the device (SADE) expedited to the Sponsor, REC and device manufacturer within 7 days of ORTU becoming aware of the event, if fatal or life threatening, or otherwise within 15 days.

Listings of adverse events will be provided to the DSMC and Sponsor when requested. The DSMC will report to the TSC and Sponsor regarding the safety profile of the Trial.

Figure 13.2.1 Adverse Event Reporting



14. DATA HANDLING AND MONITORING

14.1 Database

This study will utilise a validated system based around a fully licensed enterprise version of OpenClinica, with support services provided by OpenClinica, LLC. The study database is bespoke and hosted on the University of Oxford server with services provided through the University's Information Management Services Unit (IMSU). The server and database are protected by a number of measures including anti-virus and anti-spyware applications, firewalls, encryption technology and permissions. The database will be backed up on a daily basis. ORTU will be responsible for all data stored on the database in relation to this study.

The database and access to computers are password protected. Paper-based identifiable data at each site will be kept in a locked cabinet, in a locked or ID-access controlled area. The Data Manager will maintain a list of personnel to grant and revoke access.

14.2 Data Entry and Query Management

Patients recruited into the study are identified by their Trial Number, which cannot be traced back to personal identifiable information of the patient. Sites enrolling patients will complete the paper CRFs with aide of CRF Completion Guidelines which will be distributed to sites along with professionally printed CRFs. Upon completing the CRFs at sites, they will be sent to ORTU for data entry. ORTU will track these CRFs on a daily basis in a spread-sheet and query sites for missing CRFs. The data entry into the clinical database is performed by the designated trained ORTU staff using single data entry system. CRFs will be date-stamped and stored in a suitable locked filing cabinet.

The data stored in the clinical database will be checked for missing or unusual values and for consistency within participants over time. If any problems are identified, appropriate CRFs will be queried with relevant local site personnel for confirmation or correction as required until resolution. Should any data require changing, the ORTU staff will update the data point as per amended CRF and close the query this will be electronically tracked as an audit trail (name of reviewer, changes made and date) for the purposes of any future audit or external review. Data queries will be sent to sites on a monthly basis initially and as needed at the time of study completion or specific milestones. Details will be included in a study specific Data Management Plan).

14.3 Data Quality and Security

At the time of data entry, quality checks will be performed for missing data, illegible data, appropriate data types, incomplete data, etc. The study's Data Manager will perform quality checks of data entered and also assist with site training. Validation checks are also programmed into the database to query any discrepant data.

As part of an internal database quality check, validation of primary data will include at least confirmation of participant identity, informed consent, eligibility criteria and primary outcome data; this validation process will be carried out by the Data Manager in a subset of participants (approximately 10%).

The data will be securely stored in line with GCP standards and the data protection principles. Standard Operating Procedures (SOPs) will be followed to ensure quality control. Only staff authorised to work on this study will have access to participants' data from across all sites. The Chief Investigator and/or Principal Investigators at each individual site will facilitate access to study records for the purpose of monitoring, audits, and regulatory inspections. Participant's consent to this will be sought at the time of

enrolment into the study. ORTU will monitor recruiting sites if required in accordance with the trial Monitoring Plan which will be written based on the trial Risk Assessment.

15 DATA ANALYSIS

15.1 Description of Analysis Populations

The primary statistical analysis will be carried out on the basis of intention-to-treat (ITT). This is, after randomisation, participants will be analysed according to their allocated treatment group irrespective of what treatment they actually receive. The results from the trial will be presented as comparative summary statistics (difference in response rate or means) with 95% confidence intervals. All the tests will be done at a 5% two-sided significance level. The study results will be reported in accordance with the CONSORT 2010 statements.[56]. A full detailed statistical analysis plan will be available prior to recruitment.

15.2 Analysis of Endpoints

15.2.1 Primary Outcome

The primary efficacy end point in this study, the rate of clinically significant exacerbations over the 12-month period, will be modelled as a Poisson random variable. A Poisson regression model with an adjustment for over-dispersion will be used to compare the rate of asthma exacerbations between the two groups with log of time used as an offset variable. Further analysis will adjust for the baseline characteristics including the ACQ score, age, BMI, and sex. Intention to treat (ITT) analysis will be performed on the primary outcome on all randomised participants.

15.2.2 Secondary Outcomes

We will utilise the longitudinal analysis methods for the continuous secondary endpoints, which involve repeated measures at baseline, 3, 6, 9, and 12 months follow-up visits (including measures of lung function, composite asthma control scores and health-related quality of life measures). Mixed effect models will be used to determine whether there is an effect of the TLA device over time in these measures. For continuous variables with only baseline and 12 months data, (including lung function and carer quality of life measures) analysis will be by ANCOVA (analysis of covariance) of the 12 months outcome adjusted where appropriate for baseline and other important factors as detailed for the primary outcome.

Kaplan–Meier curves and log-rank test will be used to compare the time to first asthma exacerbation between the two groups. In addition, Cox proportional hazards models will be used to evaluate the effect of TLA device on the time to first asthma exacerbation, adjusting for the same covariates as in the primary analysis. Since the analysis of only time to first exacerbation leaves out much of the data, analysis incorporating multiple time-to-event (recurrent exacerbations) methods will also be carried out. Andersen–Gill extension of the Cox proportional regression will be used to analyse recurrent exacerbations. Using this model, the problem reduces to the analysis of time to first exacerbation, time to second exacerbation, and so on.

The proportion of participants experiencing severe exacerbations over the 12-month follow-up period will be compared using a continuity-corrected Chi-squared test. The duration of severe exacerbations, the total number of days in an exacerbation state over the 12-month follow-up period, and the number of health care utilisations will be compared between the two groups using two-sample independent t-tests.

15.2.3 Exploratory Outcomes

Sub-group analyses will include an assessment of factors associated with an improved treatment response including objective markers of bronchial and systemic allergy and inflammation, lung function, asthma and rhinitis control, quality of life and level of indoor air quality. The predictive effect of the biomarkers on exacerbations will be assessed by including the biomarker as an independent covariate together with the biomarker-treatment interaction using Poisson regression modelling in a multivariate framework (as described for the primary outcome). Additional exploration of the biomarkers as outcomes will be fully detailed in the Statistical Analysis Plan.

15.3 Procedure for Dealing with Missing, Unused and Spurious Data

In common with all longitudinal studies, we will inevitably experience the problem of missing data either in form of total non-response post-randomisation (e.g. attrition or withdrawal) or item non-response (when some but not all the required information is collected from the participants e.g. an intermittently missing endpoint due to participant not filling in the diary). However, we will attempt to minimize the missing data due to item non-response. The expected participant's dropout has already been factored into the sample size calculation. Missing data will be reported with reasons given where available and the missing data pattern explored. In order to be consistent with the ITT, missing data for the primary endpoint will be imputed using multiple imputation (MI) techniques. Our imputation model will be sufficiently general to include all the baseline variables thought to be important predictors of the response indicator of each target variable to be imputed. This will improve the validity of the imputation model under the missing at random (MAR) assumption on which the MI is based. In addition, an ignorable likelihood-based analysis will be applied for the mixed effect models.

15.4 Interim Analysis and Criteria for Early Study Termination

The DSMC will perform regular reviews of all study outcome and adverse event data, to ensure that there is no difference in rates of hospitalisation or exacerbation in either group. The DSMC will provide regular safety reports to the TSC who will advise the Sponsor accordingly. The DSMC will determine final criteria for early study termination which may be based on clear-cut evidence of worsened safety in one of the trial arms, and in the case of evidence beyond reasonable doubt of clear-cut benefit in the primary outcome measure, an effect size which would change clinical practice in the presence of the current literature and understanding of the disease area.

15. 5 Cost Effectiveness Analysis

The perspective adopted in the economic evaluation will be that of the National Health Service (NHS), therefore productivity losses and over-the-counter medication costs will not be included in the base case analysis. However, in a sensitivity analysis we will assess the impact of including these costs on the cost-effectiveness results.

15.5.1 Within-Trial Economic Evaluation

An economic evaluation adherent to guidelines for good economic evaluation practice will be undertaken integral to the main trial[54]. A within-trial cost-utility analysis will explore the incremental cost per QALY gained by TLA usage when compared to sham-TLA usage. Cost and effect results will be reported as means with standard deviations, with mean differences between the two patient groups reported alongside 95% confidence intervals (CI). For the cost analysis, given that the healthcare resource use information obtained from participants' records will contain information on all NHS-related primary and secondary care resource use occurring in the participants' usual care providers (i.e. participants' primary

care practice and local hospital trust) this information will be considered as the gold-standard when performing the cost-effectiveness analysis. We will, however, also use self-reported hospital resource use in a sensitivity analysis to see the impact on results. Depending on the amount of missing cost and quality of life data, missing data will be imputed using recommended multiple imputation methods,[37] with results from this analysis being presented as an additional sensitivity analysis. Incremental cost-effectiveness will be calculated by dividing the difference in costs by the difference in effects. Uncertainty around the incremental cost-effectiveness ratio (ICER) will be explored using non-parametric bootstrapping.[57]

15.5.2 Comparison Between Self-Reported and Routinely Collected Healthcare Resource Usage

Clinical trials are an important vehicle for capturing data on healthcare resource use, with many using patient questionnaires to obtain such information.[58] However, only a small proportion of studies have validated these by comparing self-reported to actual resource use.[59] Given that in our study healthcare resource usage will be obtained from patient-self report (through questionnaires and patient diaries) and from hospital and primary care records (i.e. HES records, patient discharge forms and primary care records), we will compare healthcare resource use obtained from records to that self-reported by patients. This supplemental analysis might then help inform future trials in asthma patients, and provide useful information on the reliability of self-completed healthcare questionnaires in asthma patients.

15.5.3 Model-Based Economic Analysis

Building on the results of the trial and subsequent cost-effectiveness analysis, a Markov model will be constructed to determine the costs and outcomes, over the life-time of the patient, of TLA usage. The model structure will be informed by reviewing modelling studies undertaken which consider the natural history of asthma, results from this trial, and from previously published studies, with experts within the team advising on the final structure of the model. The analysis will determine the cost per life year gained and cost per additional quality-adjusted life year (QALY) gained when nocturnal TLA treatment is compared to placebo. The model will be run over the patient lifetime, with costs and benefits discounted at a rate of 3.5%. In particular the model will evaluate the impact of daily adherence to TLA treatment on the cost-effectiveness analysis. Evidence gained through the qualitative study on non-adherence, and any reasons for this, will be particularly useful for this analysis. Probabilistic sensitivity analyses will be conducted to deal with uncertainty in model parameters and cost-acceptability curves presented,[60] and will be extended to consider the application of value of information (VoI) techniques, which are included in economic evaluations to inform policy decisions about the value of further research.

15.6 Qualitative Analysis

Focus Groups will be digitally recorded, transcribed verbatim and entered into NVivo 8, a qualitative software package for systematic and transparent data management. Contributions by participants will remain anonymous. An identification using a pseudonym will be assigned to each participant at recruitment. After tape recordings have been transcribed, the pseudonym will be used to refer to individuals and no “real” names will be included in any reports. Care will be taken to always ensure any direct quotes used in study reports or papers to illustrate the findings will not be directly attributable to individuals.

We will use Framework Analysis, a three stage analytic process to analyse data. This involves identifying initial themes by indexing the content of the data; this then guides the formation of a framework within which transcribed material is synthesised. Key categories are then identified to help describe the data. Finally, patterns of association are explored and attempts made to explain why those patterns occur.

15.6.1 Independent Validity of the Categories

Experienced facilitators will independently code all data. Scrutiny of the framework matrix will be sought to see if there is agreement with the categories generated. In addition, a member of the steering group, not involved in data collection, will be asked to independently read through a sample of the transcripts to generate a preliminary framework without seeing the original researchers' list. In the case of disagreement, a solution will be sought to clarify the meaning of a code/theme developed until mutual consent is reached. The aim of this stage is to attempt to enhance the validity of the development of the conceptual framework and to guard against researcher bias

16. ETHICS

The study will not be initiated before the protocol and all study relevant material such as the, informed consent forms, participant and GP information sheets have received approval / favourable opinion from the Research Ethics Committee (REC), and the respective National Health Service (NHS) Research & Development (R&D) departments. Any changes to protocol or relevant study documents will be approved by the Sponsor Should an amendment be made that requires REC approval, as defined by REC as a substantial amendment, the changes will not be instituted until the amendment has been reviewed and received approval / favourable opinion from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the REC are notified as soon as possible and an approval is requested. Minor amendments as defined by REC as non-substantial amendment, may be implemented immediately; and the REC will be informed.

The trial will be conducted in line with the Research Governance Framework. The proposed intervention is a CE marked medical device being used within its current licensing agreement, as such it is not necessary to obtain a Clinical Trials Authorisation and the MHRA have confirmed their approval will not be necessary.

16.1 Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a participants ID number on the CRF and any electronic database. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act which requires data to be anonymised as soon as it is practical to do so. The Engineering Team will retain participant data during the trial and during the post-trial provision period where appropriate, in order to provide device support and maintenance. Participant data held by the Engineering Team will be destroyed following device removal.

16.2 Informed Consent

It is the responsibility of the Investigator, or a person designated by the Investigator (if acceptable by local regulations), to obtain written informed consent from each subject participating in this study, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study using the Patient Information Sheet (PIS). The consent process will be documented in the patient's notes.

The process for obtaining participant informed consent will be in accordance with the REC guidance, and GCP and any other regulatory requirements that might be introduced. The PI/delegate and the participant or other legally authorised representative shall both sign and date the Informed Consent Form before the person can participate in the study.

The participant will keep a copy of the PIS and a signed and dated Consent Form. The original will be retained in the Trial Master File. A second copy, along with the PIS, will be filed in the participant's medical notes and a signed and dated note made in the notes of when the PIS was provided and that informed consent was obtained for the study.

The decision regarding participation in the study is entirely voluntary. The investigator or their nominee shall emphasize to them that consent regarding study participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care, or loss of benefits to which the participant is otherwise entitled. No study-specific interventions will be done before informed consent has been obtained.

The PI/delegate will inform the participant of any relevant information that becomes available during the course of the study, and will discuss with them, whether they wish to continue with the study. If applicable they will be asked to sign revised consent forms.

16.3 Declaration of Helsinki

The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 2008 the principles of Good Clinical Practice, and the Department of Health Research Governance Framework for Health and Social care, 2005.

16.4 Trial Governance

The LASER trial will be sponsored by Portsmouth Hospitals NHS Trust. ORTU will be responsible for the coordination/trial management of the trial. This study will not open to recruitment until all approvals and authorisations have been obtained. Recruitment will not commence at an individual participating site until local NHS Management approval has been obtained and all local documentation is in place and all requirements have been fulfilled.

16.4.1 Retention of Documents

Investigators must maintain at the site for at least 15 years after the study ends all required essential documents as defined in the GCP guidelines. Essential study documents include but are not limited to, those pertaining to subject files and other source data (e.g. hospital files, consultation records, laboratory reports, etc). The PI/delegate should ensure these documents are stored in a secure location and should take measures to prevent accidental or premature destruction of these documents.

The Investigator must contact the sponsor for approval prior to discarding any study-related documents, even if retention requirements have been met.

If the Investigator leaves the clinical site at which the study has been conducted, he/she or current representative must contact the Sponsor to make suitable arrangements to ensure that the study records, including a copy of the master subject log, are retained as specified above and to provide for the continuing access to the records by Sponsor representatives and Regulatory Authorities.

16.4.2 Trial Oversight

16.4.2.1 Trial Management Group

The TMG is responsible for the day-to-day management of the trial. The team is responsible for all aspects of the project (such as recruitment rate, budget management, protocol adherence, etc.) and for ensuring appropriate action is taken to safeguard trial participants and the quality of the study.

The TMG will comprise:

- Professor Anoop J Chauhan – Chief Investigator
- Dr Will Storrar – Trial Co-ordinator
- Emma Hedley – Trial Manager
- David Supple – Patient Representative

16.4.2.2 Trial Steering Committee (TSC)

The TSC consists of both independent members as well as researchers working on the trial. The role of the TSC is to provide overall supervision of the study and monitor the progress of the trial to ensure that it is being conducted in accordance with the protocol, relevant regulations and the principles of GCP. The TSC will meet at regular intervals.

The TSC will comprise:

- Independent Chair – Professor Stephen Durham
- Chief Investigator – Professor Anoop J Chauhan
- Independent Clinician - Dr William Oldfield
- Independent Clinician - Dr Simon Crowther
- Asthma UK Representative - Ms Debby Waddell
- Independent Trial Statistician – Dr. Jessica Harris
- Independent Expert / Triallist – Dr. Derrick Crump
- Trial Co-ordinator - Dr Will Storrar
- Independent Patient Representative - TBC

16.4.2.3 Data Safety Monitoring Committee (DSMC)

The DSMC is independent of the trial investigators. Its role is to review study safety data and provide advice to the TSC as to whether recruitment can continue.

The DSMC will comprise three independent members including 2 clinical specialists and a trial statistician. Full details including names will be included in the DSMC charter.

17. PATIENT PUBLIC INVOLVEMENT (PPI)

PPI input for this study has been sought from both patients with first-hand experience of living with severe asthma and a lay representative from the University of Portsmouth ENGAGE group (a group of service users and lay members with an interest in research)

Asthma UK have pledged their full support for the LASER trial. In addition to patient involvement the charity will assist with broader public engagement, raising awareness of the study.

The PPI representatives have been fully involved in the development of trial design, continually relating the theoretical aspects of the trial to pragmatic aspects of participant involvement. The PPI representatives determined the key endpoints for the trial – specifically the primary endpoint, exacerbations, recognising the significant impact that they have on the lives of patients with severe

asthma. In addition to this, PPI members advised on the timing of follow-up visits and data collection to ensure that the trial has a patient centred focus.

PPI members highlighted the importance of including participants' partners and carers in order to raise their profile and the need to improve the support for carers of patients with severe asthma.

PPI members with additional training will act as expert patients at the information events, participating in the question and answer sessions, and at the dissemination events following completion of the trial.

The TSC will have a PPI representative. Asthma UK will also be represented on the committee.

18. FINANCING AND INSURANCE

18.1 Funding

The LASER trial has been funded by the National Institute for Health Research Health Technology Assessment Programme (HTA reference 12/33/28).

18.2 Study Sponsorship

The study Sponsor is Portsmouth Hospitals NHS Trust.

18.3 Indemnity

The NHS indemnity scheme will apply for the management, design and conduct of the trial. The TLA device has a CE Mark and is covered by product liability insurance.

The device is supplied to the Sponsor by the Manufacturers Airsonett®. Under the terms of a comprehensive supply agreement the Sponsor Airsonett® will provide devices, installation and maintenance services, installing the devices directly into participant's homes. Airsonett® will provide indemnity cover for all claims arising out of or in connection with the supply of the study product or associated services, to the extent that such claims arise out of the breach, negligent performance or failure or delay in the performance of Airsonett®, and this provision is documented in the Supply agreement with the Sponsor. All complaints should be sent directly to the Sponsor representative.

19. DISSEMINATION AND PUBLICATION

19.1 Direct Access to Data

Principal Investigators at the recruiting centres will facilitate access to trial records for the purpose of monitoring, audits and DSMC reviews. Participants' informed consent will be obtained for this.

19.2 Publication

All outputs will be prepared in accordance with the NIHR HTA guidelines.

The preparation of a manuscript for publication will be the responsibility of the TMG and trial statisticians. The TSC and DSMC will have sight of the finished manuscript prior to submission.

Authorship of the primary report will include (but not be limited to) the Chief Investigator and other members of the Trial Design Team.

The results of the trial will be widely disseminated to patients, health professionals, commissioners, policy makers and the general public. Our PPI members and Asthma UK will play a key role in this maximising the use of existing networks. The trial results will be disseminated to a wide clinical audience through publication in the HTA journal series and another high impact international peer-reviewed scientific journal.

Additional outputs will include methodological and healthcare usage papers that will inform future trial design and delivery in severe asthma and other long-term conditions managed at home.

19.3 Dissemination of Results to Trial Participants:

A plain English summary of the trial findings, written in conjunction with our PPI members, will be prepared alongside scientific publications in month 42 and will be sent to all trial participants as well as being posted on the LASER Trial Website.

Participants will be sent a link to scientific publications generated from the trial (links will also be highlighted on the Website) or offered an original copy of these publications free of charge if they are not freely available on-line. Participants not wishing to access material on-line will be able to request scientific publications are sent to them by post.

Two end-of-trial dissemination events will be held to present the findings to participants and their families.

20. APPENDICES

Appendix 1

Summary table of comparative trials showing efficacy for sample size and magnitude of effect

Author	Treatment	n	Baseline Exac.Rate	Placebo Group Exac. Rate	Exac. Reduction	%	ICS Dose	Exacerbation definition
Pavord[61] 2012	Mepolizumab	621 (4 groups)	3.73 (±0.8)	**2.4 (±0.11) over 52 weeks**	1·24 vs 2·40 1.46 vs 2.40 1.15 vs 2.40	**48%** **39%** **52%**	880 µg fluticasone propionate equivalent/day, with or without maintenance OCS	Requiring OCS or ED visit + objective evidence that asthma had worsened
Haldar[62] 2009	Mepolizumab	32	5	**3.4 over 12 months**	2.0 vs 3.4	**41%**	1000-4000 BDP eqv mean 2000 µg	Requiring OCS
Green[63] 2002	Sputum Eosin guided treatment	74	2.0(3.0) in placebo group	**2.95 over 12 months**	0.95 vs 2.95	**68%**	High dose >1600 µg BDP	Requiring OCS or PEF ≤70%
Humbert[64] 2005	Omalizumab	419	2.41(1.09) in 14mnths	**0.91 [0.73, 1.14] over 28 wks**	0.68 vs 0.91 [Severe 0.24 vs 0.48]	**50%**	> 1000 µg/day BDP GINA 2002 Step 4	Requiring OCS
Hanannia[65] 2011	Omalizumab	850	1.9(1.5) in 12mnths	**0.88 over 48 wks**	0.66 vs 0.88	**25%**	>1000 µg/day FDP	Requiring OCS (or ↑dose if on maintenance)
Castro[66] 2009*	Bronchial Thermoplasty	288	Not recorded	**0.70(0.122) over 12 months**	0.48 vs 0.70	**32%**	>1000 µg/day BDP	Requiring OCS or doubling dose of ICS
Busse[67] 2008	Daclizumab	115 (3:1)	Not recorded	**Not recorded**	25% vs 47.6% at 252 days	**47%**	Mod to severe	% of participants in each group suffering an exacerbation requiring systemic corticosteroids
Pauwels[68] 1997	Symbicort	852	Not recorded	**0.91**	0.34 vs 0.91	**63%**	Low to Moderate	Requiring OCS

Appendix 2

Trial Flow Chart

laser
A breath of fresh air in asthma

Laminar Airflow in Severe asthma for Exacerbation Reduction

Study Design:

A multi-centre, randomised, double blind, placebo-controlled, parallel group trial of 12-months duration with a 4-month internal pilot.

Data collection:

Scheduled:

Visit 1: Screening Visit
- Lung Function (Spirometry +Bronchodilator Reversibility)
- Allergy testing (SPTs) (Total IgE) (Serum Specific IgE) (Eosinophils)
- Questionnaires (ACQ)

Visit 2: Randomisation Visit(0 Months)
- Lung Function (Spirometry) (F_ENO)
- Questionnaires (ACQ) (AQLQ) (EQ-5D-5L) (SNOT-22) (WPAI)
- 2 week diary submission* and review
- Carer ACQoL and WPAI (if consented)

Visits 3-6: Treatment Period (3, 6, 9 and 12 month Visits)
- Lung Function (Spirometry) (F_ENO)
- Questionnaires (ACQ) (AQLQ) (EQ-5D-5L) (SNOT-22) (WPAI)
- 2 week diary submission* and review
- TLA diary review (Device adherence) (Resource Use)

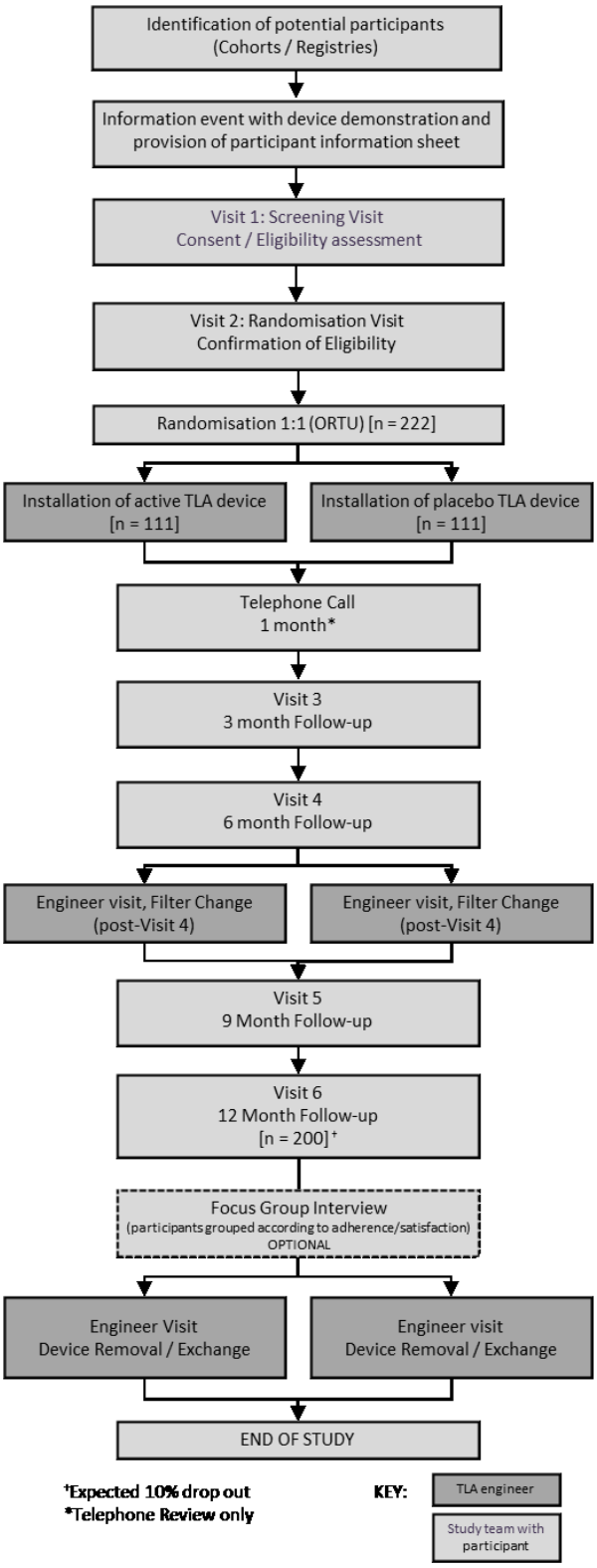
Visit 6 only:
- Bronchodilator Reversibility
- Additional Questionnaires (GETE)
- Carer ACQoL and WPAI (if consented)

TC: 1 Month Telephone Review
- Telephone Review - troubleshooting + participant reported adherence

Unscheduled:

Exacerbation data collected throughout study at 'Exacerbation Reviews'
Patients complete Exacerbation diary from onset of exacerbation

*2 week diary (Issued at visits 1 – 5)
Diary collection of:
i) Electronic Peak Flow using Vitalograph® Asma-1 device
ii) Asthma Control Diary



Appendix 3

Equivalence table for bronchial challenge testing.

Challenge Test	**Positive Result**
Direct	
Methacholine[69]	PC_{20} <8mg/ml
Histamine	PC_{20} <8mg/ml
Indirect	
Mannitol[70]	PD_{15} <635mg[i]
Exercise[69]	Fall in FEV1 of ≥10% from baseline[ii]

i Positive Result is > 15% FEV1 drop from baseline OR > 10% FEV1 drop in consecutive doses

ii Measured during recovery (up to 30mins) after achieving at least 4 minutes exercise at 80-90% of predicted maximum heart rate (predicted maximum heart rate = 220-age)

Performance of bronchial challenge testing should conform to international quality guidance.

Appendix 4

Definition of High Daily Dose of Various Inhaled Corticosteroids

Inhaled Corticosteroid	Threshold daily dose in µg considered as high in adults
Beclomethasone dipropionate	≥1000 (DPI or CFC MDI) ≥500 (HFA MDI)
Budesonide	≥800 (MDI or DPI)
Ciclesonide	≥320 (HFA MDI)
Fluticasone propionate	≥500 (HFA MDI or DPI)
Mometasone furoate	≥800 (DPI)
Triamcinolone acetonide	≥2000

CFC: Chlorofluorocarbon; DPI: Dry Powder Inhaler; HFA: Hydrofluoroalkanes; MDI: Metered Dose Inhaler.

Appendix 5

Potential interference of medications with skin prick test reactions. Adapted from[71]

Drug	Abstinence Required Before Testing
Antihistamines	
1st Generation H1-anti-histamines *Hydroxyzine*	 >2days
2nd Generation H1-anti-histamines *Cetirizine* *Loratidine* *Fexofenadine*	 7 Days 3 Days 2 Days
H2-blockers	0
Glucocorticosteroids	
Topical	>1 week (in area being tested)
Nasal	0
Inhaled	0
Systemic*	0
Other Medication	
Tricyclic Antidepressants *Doxepin* *Desipramine*	 7 days 3 Days
SSRIs *Citalopram/Fluoxetine/Sertraline*	 0
Beta-agonists	0
Anti-cholinergics	0
Leukotriene Receptor Antagonist	0
Theophylline	0

* Participants taking maintenance oral corticosteroids who have a negative skin-prick test and supportive history of atopy, proceed to specific IgE testing

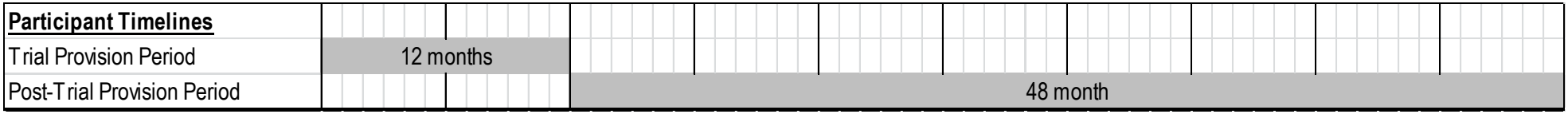
If there is any doubt as to the result of the skin prick tests when assessing eligibility criteria, please confirm allergic status with specific IgE testing (see section 11.7.3.2)

Appendix 6

Timelines Relating to Supply Agreement (not relevant to recruiting sites)

Participant Timelines:

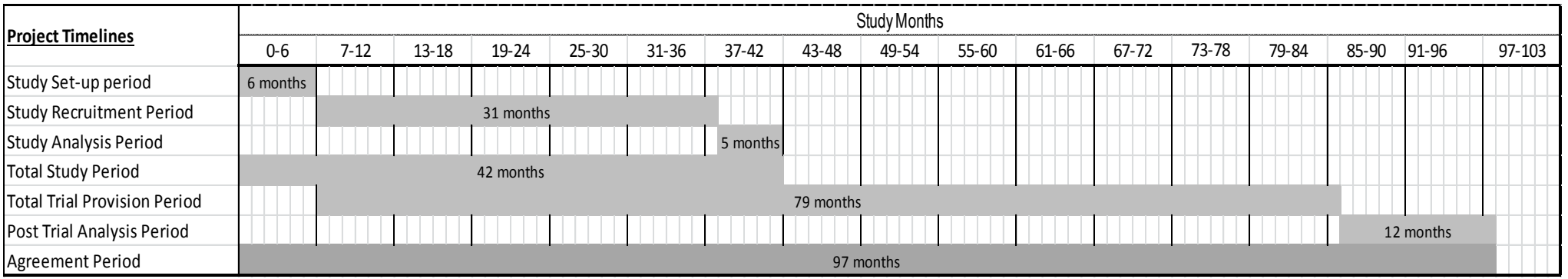
Trial Provision Period	The 12 month period commencing at Study Device or Placebo Device installation post-randomisation, during which the Participant is provided with a Study Device or Placebo Device as part of the Study. (This is synonymous with the Follow-up Period described in the Protocol).
Post-Trial Provision Period	The 4 year period commencing at least 12 months post randomisation during which the Participant is supplied with a Study Device.



Project Timelines:

Total Trial Provision Period	The entire period during which Study Devices or Placebo Devices are provided for Participants which commences at installation of the first Study Device or Placebo Device and concludes at completion of the Post-Trial Provision Period for the final Participant.
Post Trial Analysis Period	The 12 month period commencing on completion of the Total Trial Provision Period.
Study Set-up Period	The 6 month study set-up period commencing 1/10/13 and concluding 31/03/14.
Study Recruitment Period	The 31 month period of study recruitment (and treatment) commencing 1/4/14 and ending at the conclusion of the Trial Provision Period for the final Participant.
Study Analysis Period	The 5 month study analysis period commencing at the conclusion of the Study Recruitment Period.
Total Study Period	The 42 month period beginning 01/10/2013 that encompasses the Study Set-up, Recruitment and Analysis Periods.

Agreement Period	The period which commences 01/10/2013 and encompasses the Total Study Period, Total Trial Provision Period and Post-Trial Analysis Period.



21. REFERENCES

[1] Asthma UK. Living on a Knife Edge. A powerful and moving account of living with serious symptoms of asthma. 2004

[2] Holgate ST and Polosa R. The mechanisms, diagnosis and management of severe asthma in adults. Lancet. 2006;368:780-93

[3] http://www.asthma.org.uk/news-centre/facts-for-journalists/

[4] Hoskins G, McCowan C, Neville RG, Thomas GE, Smith B and Silverman S. 'Risk factors and costs associated with an asthma attack', Thorax. 2000;55:19–24

[5] Tough SC, Hessel PA, Ruff M, Green FH, Mitchell I and Butt JC. Features that distinguish those who die with asthma from community controls with asthma. J Asthma. 1998;35:657–665

[6] Turner MO, Noertjojo K, Vedal S, Bai T, Crump S and Fitzgerald JM. Risk factors for near-fatal asthma. A case-control study in hospitalized patients with asthma. Am J Respir Crit Care Med. 1998;157:1804–1809

[7] Campbell MJ, Holgate ST and Johnston SL. Trends in asthma mortality. BMJ. 1997;315:1012

[8] Bousquet J, Mantzouranis E, Cruz AA, Aït-Khaled N, Baena-Cagnani CE, Bleecker et al. Uniform definition of asthma severity, control and exacerbations: document presented for the World Health Orgaisation consultation on Severe Asthma. J Allergy Clin Immunol. 2010;126(5):926-938

[9] Rodrigo GJ, Rodrigo C and Hall JB. Acute asthma in adults: a review. Chest. 2004;125;1081-1102

[10] Nejtek VA, Brown ES, Khan DA, Moore JJ, Van Wagner J and Perantie DC. Prevalence of mood disorders and relationship to asthma severity in patients at an inner-city asthma clinic. Ann Allergy Asthma Immunol. 2001;87:129–133

[11] Asthma UK. Fighting for Breath. The hidden lives of people with severe asthma. 2010

[12] Manson SC, Brown RE, Cerulli A and Vidaurre CF. The cumulative burden of oral corticosteroid side effects and the economic implications of steroid use. Respiratory Medicine. 2009;103:975-994

[13] Humbert M, Beasley R, Ayres J, Slavin R, Hébert J, Bousquet J. et al. Benefits of Omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. Allergy. 2005;60:309-316

[14] NICE technology appraisal guidance 2012 Omalizumab for severe persistent allergic asthma 2012

[15] Department of Health. An Outcomes Strategy for COPD and Asthma in England. July 2011

[16] British Thoracic Society/Scottish Intercollegiate Guidelines Network National Guideline on the Management of Asthma. 2011

[17] Heaney LG, Brightling CE, Menzies-Gow A, Stevenson M, Niven RM; British Thoracic Society Difficult Asthma Network. Refractory asthma in the UK: cross-sectional findings from a UK multicentre registry. Thorax. 2010;65:787-794

[18] Custovic A, Taggart SC, Francis HC, Chapman MD and Woodcock A. Exposure to house dust mite allergens and the clinical activity of asthma. J Allergy Clin Immunol. 1996;98(1):64-72

[19] Tunnicliffe WS, Fletcher TJ, Hammond K, Roberts K, Custovic A, Simpson A et al. Sensitivity and exposure to indoor allergens in adults with differing asthma severity. Eur Respir J. 1999;13:654-659

[20] Langley SJ, Goldthorpe S, Craven M, Morris J, Woodcock A and Custovic A. Exposure and sensitisation to indoor allergens: Association with lung function, bronchial reactivity and exhaled nitric oxide measures in asthma. J Allergy Clin Immunol. 2003;112(2):362-368

[21] Rosenstreich DL, Eggleston P, Kattan M, Baker D, Slavin RG, Gergen P et al. The role of cockroach allergy and exposure to cockroach allergen in causing morbidity among inner-city children with asthma. NEJM. 1997;336:1356-63

[22] Green RM, Custovic A, Sanderson G, Hunter J, Johnston SL and Woodcock A. Synergism between allergens and viruses and risk of hospital admission with asthma. Case-control study. BMJ. 2002;324:763

[23] Custovic A. Simpson A, Chapman MD and Woodcock A. Allergen avoidance in the treatment of asthma and atopic disorders. Thorax. 1998;53:63-72

[24] Van Velzen E, van den Bos JW, Benckhuijsen JA, van Essel T, de Bruijn R and Aalbers R. Effect of allergen avoidance at high altitude on direct and indirect bronchial hyperresponsiveness and markers of inflammation inchildren with allergic asthma. Thorax. 1996;51:582-584

[25] Peroni DG, Boner AL, Vallone G, Antolini I, and Warner JO. Effective allergen avoidance at high altitude reduces allergen-induced hyperresponsiveness. Am J Respir Crit Care Med. 1994;149:1442–6

[26] Grootendorst DC, Dahlén SE, Van Den Bos JW, Duiverman EJ, Veselic-Charvat M, Vrijlandt EJ,et al. Benefits of high altitude allergen avoidance in atopic adolescents with moderate to severe asthma over and above treatment with high dose inhaled steroids. Clin Exp Allergy. 2001;31:400-8

[27] Gotzsche PC and Johansen HK. House Dust Mite Control Measures for Asthma. Cochrane Database of Systematic Reviews 2008

[28] Sublett JL. Effectiveness of air filters and air cleaners in allergic respiratory diseases: a review of the recent literature. Curr Allergy Asthma Rep. 2011;11:395–402

[29] Sigsgaard, T., Temperature regulated Laminair Airflow (TLA): TLA principles and practise, presented at European Academy of Allergy and Clinical Immunology 2010 Congress, London

[30] Gore RB, Boyle RJ, Hanna H, Custovic A, Gore C, Svensson P, et al. Personal allergen exposures are increased by changes in sleep position and improved by temperature controlled laminar airflow. Thorax. 2010;65:A87-A88

[31] Boyle RJ, Pedroletti C, Wickman M, Bjermer L, Valovirta E, Dahl R et al. Nocturnal Temperature Controlled Laminar Airflow for Treating Atopic Asthma: a randomised controlled trial. Thorax 2012;65:215-221

[32] Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. ERJ. 2013. doi: 10.1183/09031936.00202013

[33] Persson U, Hofmarcher T. Consulting Report. Cost Effectiveness Analysis.The Swedish Institute for Health Economics, 2012

[34] Vervloet D, Williams AE, Lloyd A and Clark TJH. Costs of managing asthma as defined by a derived Asthma Control Test™ score in seven European countries. Eur Respir Rv. 2006;15:17-23

[35] Brodtkorb TH, Zetterström O, and Tinghög G. Cost-effectiveness of clear air administered to the breathing zone in allergic asthma. Clin Respir J. 2010;4:104-110

[36] Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW et al. An Official American Thoracic Society/European Respiratory Society Statement: Asthma Control and Exacerbations.

Standardizing Endpoints for Clinical Asthma Trials and Clinical Practice. Am J Respir Crit Care Med 2009;180:59-99

[37] Royston P. Multiple imputation of missing values. Stata Journal 2004;4:227-241

[38] Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A et al. ATS/ERS Task Force: Standardisation of Lung Function Testing. Standardisation of Spirometry. Eur Respir J. 26: 319-338. 2005.

[39] ATS/ERS Recommendations for Standardized Procedures for the Online and Offline Measurement of Exhaled Lower Respiratory Nitric Oxide and Nasal Nitric Oxide. Am J Respir Crit Care Med Vol 171. Pp 912-930, 2005

[40] Bernstein I, Li J, Bernstein D, Hamilton R, Spector S, Tan R et al. American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology. Allergy diagnostic testing: an updated practice parameter. Ann Allergy Asthma Immunol.2008;100:S1-148

[41] Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ and King DR. Development and validation of a questionnaire to measure asthma control. ERJ. 1999;4:902-7

[42] Juniper EF, Guyatt GH, Ferrie PJ and Griffith LE. Measuring Quality of Life in Asthma. American Review of Respiratory Disease. 1993;4:832-8

[43] Juniper EF, Guyatt GH, Willan A and Griffith LE. Determining a minimal important change in a disease-specific quality of life questionnaire. J Clin Epidemiol. 1994;47:81-7

[44] EQ-5D-5L User Guide: Basic information on how to use the EQ-5D-5L instrument. Euroqol Group, 2011 http://www.euroqol.org/fileadmin/user_upload/Documenten/PDF/Folders_Flyers/UserGuide_EQ-5D-5L_v2.0_October_2013.pdf

[45] Pickard l, Wilke C, Jung E, Patel S, Stavem K and Lee T. Use of a preference-based measure of health (EQ-5D) in COPD and asthma. RespMedicine 2008;102:519-536.Curtis L. Unit costs of health and social care 2012. Canterbury: Personal Social Services Research Unit, 2012

[46] Hopkins C, Gillett S, Slack R, Lund VJ and Browne JP. Psychometric validity of the 22-item Sinonasal Outcome Test.Clin Otolaryngol.2009;34:447–54

[47] Lloyd A, Turk F, Leighton T and Canonica GW. Psychometric evaluation of Global Evaluation of Treatment Effectiveness: a tool to assess patients with moderate-to-severe allergic asthma. Journal of Medical Economics.2007;10:285-96

[48] Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. PharmacoEconomics 1993; 4(5):353-65.

[49] Juniper EF, O'Byrne PM, Ferrie PJ, King DR and Roberts JN. Measuring Asthma Control. AJRCCM. 2000;162:1330-4

[50] Dolan P, Gudex C, Kind P and Williams A. A social tariff for EuroQol: Results from a UK general population survey. Centre for Health Economics: University of York, 1995

[51] Curtis L. Unit costs of health and social care. Canterbury: Personal Social Services Research Unit, 2012

[52] Department of Health. National Health Service Reference Costs 2011/12. http://www.dh.gov.uk/health/2012/11/2011-12-reference-costs/ London : Department of Health, 2012

[53] Joint Formulary Committee. British National Formulary (online). http://www.medicinescomplete.com/ London: BMJ Group and Pharmaceutical Press, 2013

[54] Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ and Stoddart GL. Methods for the Economic Evaluation of Health Care Programmes. Oxford: Oxford University Press, 2005

[55] Gore RB, Hanna H, Custovic A, Gore C, Svensson P et al. Effect of a novel Temperature controlled Laminar Airflow device on personal breathing zone cat allergen exposure. Allergy. 2010; 65 s92: 686

[56] Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMJ 2010;340:c332.

[57] Briggs A, Gray A. The distribution of healthcare costs and their statistical analysis for economic evaluation. J Health Serv Res Policy. 1998;3:233-45

[58] DIRUM. Database of Instruments for Resource Use Measurement. http://www.dirum.org/about/ DIRUM, 2012

[59] Ridyard C, Hughes D. Methods for the collection of resource use data within clinical trials: A systematic review of trials funded by the UK Health Technology Assessment programme. Value in Health 2010;13:867-72

[60] Claxton K, Sculpher M, McCabe C, Briggs A, Akehurst R, Buxton et al. Probabilistic sensitivity analysis for NICE technology assessment: not an optional extra. Health Economics 2005;14:339-347

[61] Pavord I, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. Lancet 2012;380:651–59

[62] Haldar P, Brightling CE, Hargadon B, Gupta S, Monteiro W, Sousa A et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. NEJM 2009;360:973-984

[63] Green RH, Brightling CE, McKenna S, Hargadon B, Parker D, Bradding P et al. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. The Lancet 2002;360:1715-21

[64] Humbert M, Beasley R, Ayres J, Slavin R, Hébert J, Bousquet J,et al. Benefits of Omalizumab as add-on therapy. Allergy 2005;60:309-316 (The INNOVATE study)

[65] Hanania NA, Alpan O, Hamilos DL, Condemi JJ, Reyes-Rivera I, Zhu J et al. Omalizumab in severe allergic asthma inadequately controlled with standard therapy. Annals of Internal Medicine 2011;154:573-582

[66] Castro M, Rubin AS, Laviolette M, Fiterman J, De Andrade Lima M, Shah PL et al. Effectiveness and safety of bronchial thermoplasty in the treatment of severe asthma (AIR 2). Am J Respir Crit Care Med 2009;181:116-2

[67] Busse WW, Israel E, Nelson HS, Baker JW, Charous BL, Young DY et al. Daclizumab Improves Asthma Control in Patients with Moderate to Severe Persistent Asthma. 2008 Am J Respir Crit Care Med;178:1002–1008

[68] Pauwels RA, Löfdahl CG, Postma DS, Tattersfield AE, O'Byrne P, Barnes PJ et al. Effect of inhaled formoterol and budesonide on exacerbations of asthma. NEJM 1997;337(20):1405-1411 (The FACET study)

[69] Crapo RO, Casaburi R, Coates AL, Enright PL, Hankinson JL Irvin CG,et al. Guidelines for Methacholine and Exercise ChallengeTesting-1999. Am J Respir Crit Care Med 2000; 162 (1): 309-329

[70] Anderson SD, Brannan J, Spring J, Spalding N, Rodwell LT, Chan K,A et al. A new method for bronchial-provocation testing in asthmatic subjects using a dry powder of mannitol. Am J Respir Crit Care Med. 1997;156(3 Pt 1):758-65

[71] Heinzerling L, Mari A, Bergmann K-C, Bresciani M, Burbach G, Darsow U et al. The skin prick test – European standards. Clin Transl Allergy. 2013; 3: 3