UNIVERSITY OF PORTSMOUTH

School of Health Science and Social Work

TEMPERATURE CONTROLLED LAMINAR AIRFLOW TREATMENT FOR PATIENTS WITH SEVERE ALLERGIC ASTHMA

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This thesis is submitted in partial fulfilment of the requirements for the award of the degree of Doctor of Medicine of the University of Portsmouth

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laser
A breath of fresh air in asthma

ABSTRACT

Background

Severe asthma exacerbations are costly to patients and the NHS and occur frequently in patients with severe allergic asthma.

Objective

To ascertain whether the use of a temperature-controlled laminar airflow (TLA) device (Airsonett®) over a 12-month period can reduce the frequency of severe exacerbations and improve asthma control and quality of life as compared to a placebo device in adults with severe allergic asthma.

Trial Design

A mixed methods, multi-centre, randomised, double-blind, placebo-controlled, parallel group, trial design.

Participants

Adults (16-75 years) with severe, poorly-controlled, exacerbation-prone, asthma sensitised to a perennial indoor aeroallergen.

Main Outcome Measures

PRIMARY OUTCOME:

Frequency of severe asthma exacerbations occurring within the 12-month follow-up period, defined as 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.

SECONDARY OUTCOMES:

Changes in asthma control, lung function, asthma-specific and global quality of life for participants and device acceptability.

Results

240 participants were randomised. 119 Active Treatment : 121 Placebo. 202 participants (84%) reported use of the device for 9-12 months. Qualitative analyses showed high levels of acceptability.

The mean rate of severe exacerbations did not differ between groups (Active: Mean 1.39 (SD 1.57), Placebo: Mean 1.48 (SD 2.03) Risk Ratio 0.92, 95% CI 0.66-1.27, p=0.616). There were no significant differences in secondary outcomes for lung function, except for a reduction in mean daily peak expiratory flow (difference 14.7 L/min, SD 7.35, 95% CI 0.32-29.1 L/min, p=0.045) in the active device, and no differences in asthma control or airway inflammation. There was no difference in generic or disease-specific health-related quality of life overall, although statistically significant higher quality of life at month 6 was observed.

Conclusions

Within the limits of the data, no consistent benefits of the active device were demonstrated.

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ABBREVIATIONS

ACD	Asthma Control Diary
ACQ	7-Point Asthma Control 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
BT	Bronchial Thermoplasty
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
CRN	Clinical Research Network
DoH	Department of Health
ED	Emergency Department
EQ5D-5L	EuroQol 5-Dimension 5-Level Questionnaire
FDP	Fluticasone Dipropionate
$FEF_{25-50\%}$	Forced Expiratory Flow Rate (25-50%)
F_ENO	Fraction of Exhaled Nitric Oxide
FEV_1	Forced Expiratory Volume (in 1 second)
FU	Follow-up Visit Form
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
HRQoL	Health Related Quality of Life
HTA	Health Technology Assessment
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 Adjustable Reliever Therapy
NHS	National Health Service
NIV	Non-Invasive Ventilation
NRAD	National Review of Asthma Deaths
OCS	Oral Corticosteroid
ORTU	Oxford Respiratory Trials Unit
PC20	Provocation Concentration causing 20% drop in FEV_1
PED	Participant Exacerbation Diary
PEF	Peak Expiratory Flow
PIS	Participant Information Sheet
PPI	Patient Public Involvement
QA	Quality Assurance
QoL	Quality of Life
R&D	Research and Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
REV	Exacerbation Review Form

SADE	Serious Adverse Device Effect
SAC	Specialist Asthma Centre
SAE	Serious Adverse Event
SEK	Swedish Krona
SMP	Self-Management Plan
SMS	Short Messaging Service
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
WHO	World Health Organisation
WPAI(A)	Work Productivity and Activity Impairment (Asthma)

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DECLARATION

Whilst registered as a candidate for the above degree, I have not been registered for any other research award. The results and conclusions embodied in this thesis are the work of the named candidate and have not been submitted for any other academic award.

Word Count: 34,071

DISSEMINATION

Storrar et al. Temperature-controlled laminar airflow in severe asthma for exacerbation reduction (The LASER Trial): study protocol for a randomised controlled trial. Trials (2016) 17:15.

Storrar et al. Recruitment to clinical trials - the use of social media. Trials (2015) 16(Suppl 2):O77. [ORAL PRESENTATION AND POSTER]

Storrar et al. Early qualitative analysis to enhance trial processes. Trials (2015) 16(Suppl 2):P73. [POSTER]

Storrar et al. Educational information events to enhance recruitment to clinical research trials. Eur Resp J (2015) 46 (suppl 59) [POSTER]

CHAPTER 1. INTRODUCTION

1.1. BACKGROUND AND RATIONALE

1.1.1. THE BURDEN OF SEVERE ASTHMA

1.1.1.1. 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. (Asthma UK 2004) (Holgate and Polosa 2006). The burden of severe asthma on the NHS is enormous, accounting for 80% of total asthma cost (£1 billion) (Asthma UK 2017) with frequent exacerbations and expensive medications generating much of this cost (Hoskins et al 2000). Reported UK asthma deaths are amongst the highest in Europe and rates have plateaued at between 1000 and 1200/year since 2000 (NRAD 2014) (DoH 2011). Those whose asthma remains poorly-controlled face the greatest risk (Tough et al 1998) (Turner et al 1998) (Campbell et al 1997). Patients with severe asthma bear the greatest burden of asthma morbidity. They experience more frequent and severe exacerbations (Bousquet et al 2010) which reduce their quality of life, impair their ability to work and place an enormous burden of anxiety on them and their families (Rodrigo et al 2004). There is also an increased risk of significant depression (Nejtek et al 2001). 1 in 5 asthmatics in the UK report serious concerns that their next asthma attack will be fatal (Asthma UK 2004). 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 (Asthma UK 2010).

1.1.1.2. THE UNMET NEED IN SEVERE ASTHMA

Current treatments including oral corticosteroids, 'steroid-sparing' immunosuppressants and monoclonal antibody therapies often have limited efficacy and 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 (Manson et al 2009). The anti-IgE treatment Omalizumab© has been shown to reduce exacerbations by up to 50% (Humbert et al 2005) and improve quality of life in severe allergic asthma but costs up to £26,640 per year (NICE 2012). 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 when its use is limited to those with severe, persistent, confirmed allergic, IgE-mediated, asthma experiencing 4 or more severe exacerbations in the preceding 12 months (NICE 2012). A large

number of patients are therefore left with a significant unmet clinical need and a specific requirement for therapies which reduce systemic steroid exposure.

1.1.1.3. National/International Strategies to Improve Asthma Care

The Department of Health "Outcomes Strategy for COPD and Asthma" (DoH 2011) recognises the huge burden that poorly controlled asthma places on people's lives and the NHS. It also describes the political commitment to improve asthma control and reduce asthma related emergency healthcare needs and deaths. The 2014 British Thoracic Society (BTS) and Scottish Intercollegiate Guidelines Network (SIGN) national asthma guidelines and 2010 WHO consultation on severe asthma (BTS/SIGN 2014) (Bousquet et al 2010) 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. In its research strategy for 2016 – 2021, Asthma UK identifies the development of new treatments as a priority for improving clinical outcomes and patient well-being and reducing the cost of treating severe asthma within the NHS. It also identifies the need to gain a better understanding of the impact of exposure to substances known to trigger asthma, and the impact of strategies that regulate and control this exposure, as a key priority.

1.1.2. The Significance of Allergen Exposure and Environmental Interventions

More than 70% of people with severe asthma are sensitised to common aeroallergens and/or moulds (Heaney et al 2010,) the level of allergen exposure determining symptom severity; those exposed to high allergen levels are at increased risk of exacerbations and hospital admissions. (Custovic et al 1996,) (Tunnicliffe et al 1999,) (Langley et al 2003,) (Rosenstreich et al 1997). Domestic exposure to allergens is also known to act synergistically with viruses in sensitised patients to increase the risk and severity of exacerbations (Green et al 2002). Allergen avoidance has been widely recognised as a logical way for treating these patients (Custovic et al 1998). 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 (Van Velzen et al 1996,) (Peroni et al 1994,) (Grootendorst et al 2001). Unfortunately, effective methods of allergen reduction have proved elusive (Gotzsche and Johansen 2008) (Sublett 2011) 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.

1.1.2.1. 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 (Spilak et al 2016). Proof-

of-concept studies have shown that 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 30-fold (p=0.043) and significantly reduces the increase in number of particles generated when turning in bed for all particle sizes (Gore et al 2010). When compared to a best in class traditional air cleaner, TLA is able to reduce exposure to potential allergens by a further 99% (Sigsgaard 2010). We postulated that this highly significant reduction in nocturnal exposure, targeted to the breathing zone, explained why TLA might succeed in an area where so many other measures, including traditional air cleaners, had failed.

1.1.2.2. CURRENT EVIDENCE OF BENEFIT WITH TLA THERAPY

A small randomised controlled cross-over trial in Sweden (Pedroletti et al 2009,) randomised 22 patients (age range 12-33 years) to either an active or placebo TLA device for 10 weeks, followed by a 2-week wash-out phase before switching to the opposite treatment group for another 10 weeks. The primary outcome measure was mean change in quality of life, measured as mini-AQLQ score. Bronchial inflammation (F_ENO) and lung function (spirometry) were also measured. Treatment with the active TLA device resulted in an improved quality of life score that was significant compared with the placebo group (difference in mean score change 0.54; p<0.05). Significantly lower values of F_ENO were also detected during the active treatment period (mean −6.95ppb; p<0.05).

These findings were replicated in a larger pan-European multicentre 12-month randomised-controlled trial (Boyle et al 2012) (n=282, age range 7-70 years). Treatment with an active TLA device when compared to placebo improved asthma-related quality of life and bronchial inflammation (F_ENO). In this trial the greatest benefit was seen in the more severe asthma patients requiring higher intensity treatment (GINA Step 4) and with poorly controlled asthma (Asthma Control Questionnaire <19). GINA Step 4 is consistent with ATS/ERS Severe Asthma Guideline definitions 2014 (Chung et al 2014) and BTS/SIGN Guideline treatment Step 4 (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 of the study data showed a decreased exacerbation rate in the 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). The trial was powered to detect a difference in asthma-related quality of life and did not specifically include patients at risk of exacerbations (average annual rate of exacerbations in the study population was only 0.2 exacerbations/year).

In a small German trial of 32 patients (Schauer et al 2015) with poorly controlled asthma (GINA 3-4) prospective medical records data on exacerbations and asthma control were compared in the year before and after introduction of TLA treatment. This study found a reduction in the annual rate of exacerbations (3.57 before and 1.30 after; p=0.00013) after the introduction of the TLA device.

Improvements were also seen in asthma control, healthcare utilisation and bronchial hyper-reactivity after introduction of the TLA device.

A further, pragmatic, patient-centred, RCT of this novel non-pharmacological treatment in patients with severe, exacerbation-prone, allergic asthma was thus warranted in order to determine whether TLA treatment is effective in reducing the frequency of asthma exacerbations in this patient group.

1.1.3. The LASER Trial

The LASER Trial (Temperature-controlled **L**aminar **A**irflow in **S**evere Asthma for **E**xacerbation **R**eduction) was designed 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 in the UK.

A funding grant of £1.2m was awarded by the National Institute for Health Research Health Technology Assessment programme to the research team at Portsmouth Hospitals NHS Trust (NIHR HTA Project Number 12/33/28) to deliver the Trial. The Trial was sponsored by Portsmouth Hospitals NHS Trust.

1.1.3.1 Objectives

The LASER Trial was designed to meet the following objectives:

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, ≥30mg prednisolone or equivalent daily or ≥50% increase in dose if maintenance 30mg prednisolone or above, for 3 or more days).

Secondary Objectives

- To assess the impact of nocturnal TLA treatment on asthma control, including:

1. 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.

2. 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.

- To evaluate the impact of TLA treatment on education/work days lost.

- To qualitatively evaluate the perceptions, values and opinions of the device to identify potential modifications to improve participant acceptance and to inform future implementation of the device within the NHS setting.

CHAPTER 2. METHODS

2.1 TRIAL DESIGN

The LASER trial was designed exclusively to meet the objectives previously described (See 1.1.3.1). The Trial design determined to best meet these objectives was a mixed-methods, multi-centre, randomised, double blind, placebo comparator, parallel group trial design, with each individual participant trialling the active or placebo device for 12 months.

A placebo comparator was 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. Participants were randomised in a 1:1 ratio to receive either an active treatment device, or a placebo device. Throughout the trial, participants in both treatment arms received standard asthma care in accordance with the national BTS/SIGN guidelines for the management of asthma in adults (BTS/SIGN 2014).

Figure 2.1 presents a simple overview of the trial design, highlighting the 6 Study Visits (1. Screening Visit, 2. Randomisation Visit, 3. – 6. Follow-up Visit at 3, 6, 9 and 12 months). The full trial flow chart and data collected at each of these Study Visits are summarised in **Figure 2.2** and **Table 2.1**, presented in full in **Appendix F**, and explained throughout this Methods chapter.

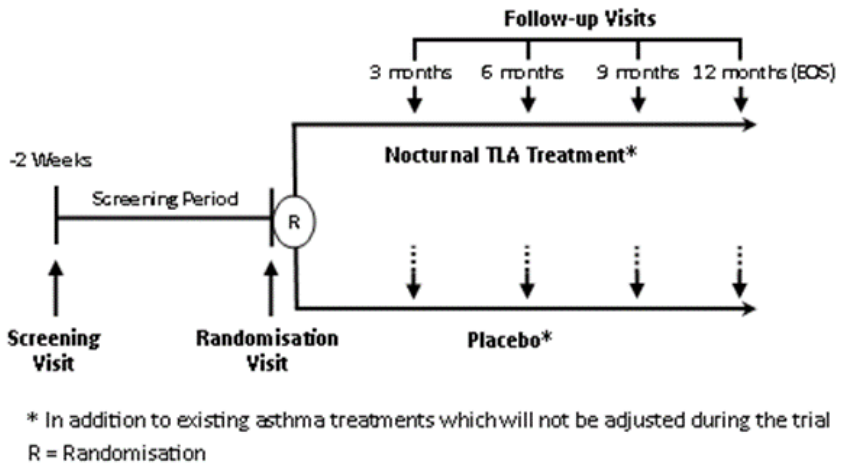


Figure 2.1 Trial Design

2.1.1 TRIAL PROTOCOL

Figure 2.2 consolidates and summarises the major content of the trial protocol into a simple flowchart. The major activities comprising the trial are described below. The data collected at these visits are listed in **Table 2.1**.

- **Participant recruitment** (Chapter 3)

- **Study visits**

  Participants were required to attend the following 6 study visits to collect the scheduled data indicated in **Table 2.2**.

  1. Screening Visit (Section 2.6.1)

  Purpose of data collection = Screen participant against trial inclusion and exclusion criteria (Section 2.2.2 and Section 2.2.3)

  2. Randomisation Visit (Section 2.6.2)

  Purpose of data collection = Assign participant to active or placebo device treatment arm (Section 2.7.2)

  3. 3-month Follow-up Visit

  4. 6-month Follow-up Visit

  5. 9-month Follow-up Visit

  6. 12-month Follow-up Visit

  Common purpose of Study Visits 3 – 6 = Secondary outcome data collection (Section 2.4.2)

- **Unscheduled data collection**

  Purpose of data collection = Primary outcome data collection (Section 2.4.1)

- **Focus Group Interviews**

  Purpose of data collection = Capture individual's perceptions, expectations and meaning to explore acceptance, level of personal control, motivation and usefulness of the TLA device (Section 2.10.3.2)

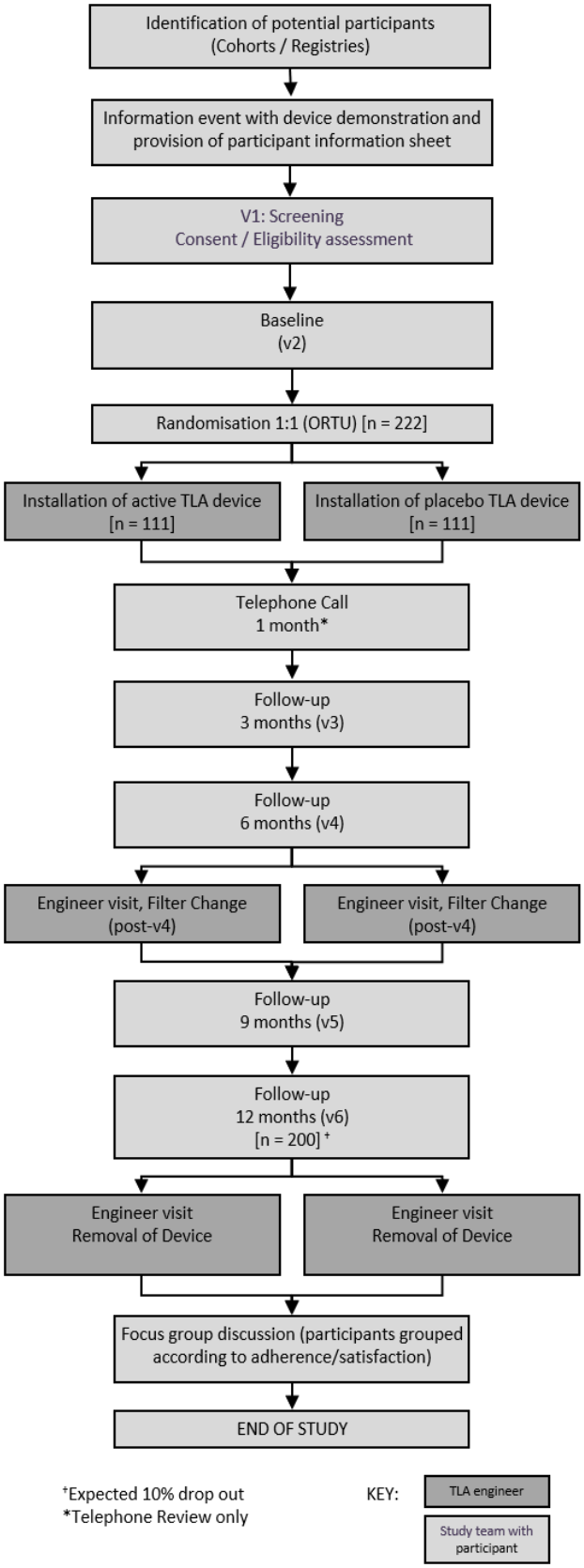


Figure 2.2 LASER Trial Flowchart

Table 2.1 Data collected at each visit

Scheduled data	
Visit 1: Screening	Lung Function (Spirometry + Bronchodilator Reversibility)(F_ENO)
	Allergy testing (Skin Prick Tests) (Total IgE) (Serum Specific IgE)
	Questionnaires (ACQ)
Visit 2: Baseline / Randomisation	Lung Function (Spirometry + Bronchodilator Reversibility)
	Questionnaires (ACQ) (AQLQ) (EQ-5D-5L) (SNOT-22)(WPAI)
	2 week diary submission*
Visits 3 – 6: Follow-up Visits (Treatment period)	Lung Function (Spirometry) (F_ENO)
	Questionnaires (ACQ) (AQLQ) (ED-5D-5L) (SNOT-22) (WPAI)
	2 week diary submission*
	TLA diary review of device adherence
Visit 6 only	Lung Function (Bronchodilator Reversibility)
	Additional Questionnaire (GETE)
Unscheduled data	
Exacerbation history collected throughout study at "Exacerbation Reviews"	
Continuous daily "TLA diary" completion including daily corticosteroid dose	
Exacerbation history also recorded at Follow-up Visits	

*2 week diary (issued at visits 1-5)
Diary collection of:

i) Twice Daily Electronic Peak Flow Recordings
ii) Symptoms (paper diary) documenting daytime/nocturnal asthma symptoms and reliever medication use.

2.2 Eligibility and Inclusion/Exclusion criteria

2.2.1 Participants

The chosen eligibility criteria closely mirror those of previous studies reporting the rates of severe exacerbation used in the statistical models of this trial (see Appendix G).

2.2.2 Inclusion Criteria

Potential participants had to meet ALL of the following inclusion criteria by 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 >15% during the baseline 2-week period or a variability in forced expiratory volume in 1s (FEV_1) of >20% across clinic visits within the preceding 12 months, with concomitant evidence of airflow obstruction (FEV_1/FVC ratio <70%, where FVC is forced vital capacity);
  - 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 causing at least a 20% reduction in FEV_1 (PC_{20}) of ≤8mg/ml or equivalent test (see Appendix H).

- **Severe asthma**

  - Requirement for high-dose inhaled corticosteroids (ICS) (≥1000µg/day beclomethasone (BDP) or equivalent – see Appendix I) 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 excluded any interim need for short-term steroid bursts to treat exacerbations.

- **Poorly controlled asthma** demonstrated by <u>BOTH</u>:

  - ≥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;

- Asthma Control Questionnaire (ACQ) 7-point score >1 at Screening Visit 1 and Randomisation Visit 2.

- **Atopic status**

  - Sensitisation to ≥1 perennial indoor aeroallergen (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 against Der p 1, Der f 1, Asp f 1, Alt a 1, Cla h 1, Fel d 1 or Can f 1 (wheal diameter ≥3mm more than negative control) or specific IgE ≥0.35 IU/L determined by blood test.

- **Recent medical stability**

  - 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 and in the period between Screening Visit 1 and Randomisation Visit 2 (the Screening Period). Participants suffering a severe exacerbation during the Screening Period were rescreened 2 weeks after returning to their maintenance asthma medications.

- **Adherence**

  - 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.

2.2.3 Exclusion Criteria

Potential participants who met **ANY** of the following exclusion criteria were excluded from participating in the study:

- Current smokers or ex-smokers abstinent for <6 months.
- 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 within the follow-up period.
- Documented poor treatment adherence.
- 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 it is known that this impairs 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.
- Participants currently taking part in other interventional respiratory clinical trials.

2.2.4 CENTRES AND CARE PROVIDERS

The feasibilities of 25 secondary care providers as Recruiting Centres for the LASER trial were considered. The 14 sites listed in **Table 2.2** were selected, all with trial teams embedded within Respiratory Departments. Each of these Recruiting Centres activated the trial at different dates during the study period and these activation dates are also shown in **Table 2.2**.

Table 2.2 Recruiting Centres and trial activation dates

Site	Date of activation
Portsmouth, Trial Lead Site	7 May 2014
Aintree	17 Jun 2014
Heartlands Birmingham	26 Jun 2014
Leicester	09 Jul 2014
Southampton	09 Jul 2014
Bradford	09 Sep 2014
Royal Liverpool	20 Jan 2015

St Georges	22 Jan 2015
Chester	03 Feb 2015
Oxford	26 Feb 2015
Hull	02 Apr 2015
Maidstone	07 Jul 2015
Queen Elizabeth Birmingham	30 Jul 2015
Belfast	26 Aug 2015

2.3. INTERVENTIONS

2.3.1. TREATMENT VERSUS COMPARATOR

2.3.1.1 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 the air (0·5-0·8°C) 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 and thereby reducing allergen exposure without creating draft or dehydration. 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.

Figure 2.3 The temperature-controlled Laminar Airflow (TLA) device, Airsonett®

2.3.1.2 Placebo Devices

The placebo devices are adjusted to deliver isothermal air instead of slightly cooled air, and holes in the filter effectively allow the air to bypass it whilst still maintaining an equivalent sound and airflow level to an active device. This allows the placebo device to deliver non-laminar, non-filtered, non-descending, isothermal air which, when mixed with the warm body convection, ascends towards the ceiling and thus has 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-monthly intervals.

2.3.2 Asthma Care During the Trial

2.3.2.1 Treatments when Stable

All participants were evaluated by clinicians with expertise in severe asthma during the study follow-up visits (Study Visits 3, 4, 5 and 6). These experts were able to identify and exclude alternative or co-morbid pathologies contributing to poor asthma control and confirm treatment adherence.

No adjustment or reduction of asthma medications (excluding antihistamines and nasal corticosteroids) were 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 was recorded at each follow-up visit (including the use of over-the-counter medications).

Those participants using variable "Maintenance ± Adjustable Reliever Therapy (MART)", which combines inhaled corticosteroid (ICS) and bronchodilator therapy in a single inhaler, were converted to a fixed dose regimen (preferably without changing inhalers) and an alternative short-acting bronchodilator (e.g. Salbutamol, Terbutaline) by the site team for the duration of the trial. A LASER "BDP equivalent" dose calculator was developed to allow Centres to easily calculate the BDP equivalent of their inhaled corticosteroid based on the dose and frequency of use, and on known pharmacokinetics of all available inhaled therapy.

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

2.3.2.2 ASTHMA EXACERBATIONS

Asthma exacerbations were managed following best clinical practice in the appropriate setting following the national BTS/SIGN guidelines (BTS/SIGN 2014)..

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

Participants who self-managed their oral corticosteroids were instructed to contact 999 if they required urgent medical attention or to self-manage in the community as directed by their agreed self-management plan if they did not require urgent medical attention.

Participants reported severe exacerbations to their local site trial team as soon as possible after exacerbation onset (Section 2.4.1.1).

Clinicians prescribed the process for reducing and ultimately stopping corticosteroid treatment and returning to normal maintenance dose after each exacerbation, determined by individual patient need.

2.3.3 INTERVENTION STANDARDISATION

Prior to shipping, the manufacturer (Airsonett®) ensured all devices were quality checked to CE standard on air temperature regulation, airflow and breathing zone particle reduction metrics. They also provided all the required quality control documentation.

2.3.4 ADHERENCE MONITORING

To simplify adherence to the intervention, study devices were programmed at installation to automatically turn on for a minimum of 10 hours to cover the participants' normal sleeping hours. This could be overridden by the participant should they wish to start the treatment at a different time or turn off the device. Participants were allowed to increase their usage of the device, e.g. for daytime naps. All episodes of usage of the device was documented in the daily participant-completed TLA diary (Section 2.10.2.2).

2.4 OUTCOMES

The trial used validated, standardised primary and secondary outcomes for clinical asthma trials recommended by the American and European Thoracic Societies and endorsed by the COMET initiative (Reddel et al 2009). Comparison of data at multiple time-points was used to assess the magnitude and rate of treatment response and variation in level of control.

2.4.1 PRIMARY OUTCOME

There was one primary outcome:

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

Severe asthma exacerbations are defined in accordance with ATS/ERS guidelines (Reddel et al 2009) 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 are treated as separate severe exacerbations.

2.4.1.1 MEASUREMENT OF PRIMARY OUTCOME

Participants were asked to start an exacerbation diary (PED) when exceeding the 'exacerbation-dose' threshold of systemic corticosteroids individually defined for each participant during Randomisation Visit 2. The PED included PEF measurements (using the trial electronic PEF device), oral corticosteroid dose, reliever medication use, and nocturnal asthma symptoms. Participants were asked to report severe exacerbations to their local site trial team as soon as possible after onset via a dedicated telephone line or a secure NHS e-mail account. Wherever possible, participants were asked to attend an Exacerbation Review with their local trial team within 72 hours to corroborate the exacerbation, at which the local trial team completed an Exacerbation Review Form (REV) using the PED. An exacerbation was confirmed if the participant met the trial definition for a severe asthma exacerbation corroborated by any one or more of the following additional criteria:

1. An associated decrease in morning PEF compared to maximum morning PEF achieved at baseline.

2. A 50 % increase in reliever medication on at least 2 of 3 successive days compared to baseline.

3. Increased nocturnal wakening.

If participants were not able to attend an Exacerbation Review, the PED was collected at the next follow-up visit.

Information about exacerbations was also collected from the participant-completed daily diary in which they recorded their daily corticosteroid dose (TLA Diary), and from Follow-up Visit forms (FU) completed by the clinician delivering each follow-up visit.

Details about how these various sources of exacerbation data were combined to make a useable primary outcome are detailed in Section 2.11.2.2.

2.4.2 SECONDARY OUTCOMES

2.4.2.1 QUANTITATIVE

The quantitative secondary outcomes of the LASER trial were:

1. Asthma control

To assess the impact of nocturnal TLA treatment on asthma control.

2. Quality of life

To ascertain the effect of TLA treatment on quality of life.

3. Impact

To evaluate the impact of TLA treatment on work productivity and activity impairment.

4. Treatment Effect

To determine participant and physician perception of treatment effect.

1) Asthma Control

The following indicators of <u>current</u> asthma control were determined and recorded at the Randomisation Visit (as baseline data) and each follow-up visit (3, 6, 9 and 12 months during trial as intervention data):

- Lung function measures
  - Pre-bronchodilator FEV_1
  - Mean morning pre-bronchodilator Peak Expiratory Flow (PEF) Rate over 2-weeks preceding follow-up visits
  - Fractional concentration of exhaled Nitric Oxide (F_ENO)
- Asthma Control Questionnaire (ACQ) score
- Asthma Control Diary (ACD) score over 2-weeks preceding follow-up visits
- Sino-Nasal Outcome Test (SNOT-22) score

The following indicators of risk of <u>future</u> adverse asthma outcomes were also determined and recorded at these visits:

- Severe exacerbations (see Section 2.3.2.2 *'Asthma Exacerbations'* for definition)
- Systemic corticosteroid use over the 12 month follow-up period

- Post-bronchodilator FEV_1 at 12-month follow-up visit

2) Quality of life

The following health-related participant quality of life scores were determined and recorded at the Randomisation Visit (as baseline data) and each follow-up visit (3, 6, 9 and 12 months, as intervention data):

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

3) Impact

- Work Productivity and Activity Impairment (WPAI) score

The WPAI score was determined and recorded at the Randomisation Visit (as baseline data) and each follow-up visit (3, 6, 9 and 12 months, as intervention data)

4) Treatment Effect

- Global Evaluation of Treatment Effect

The Global Evaluation of Treatment Effect (GETE) score was collected at the 12 month follow up visit for both participants and physicians.

2.4.2.2 QUALITATIVE

In addition to the quantitative secondary outcomes described above, there was one qualitative secondary outcome:

Acceptability

To qualitatively evaluate the trial participant's perceptions, values and opinions of the trial process and TLA device to identify potential modifications to improve participant acceptance and to inform future implementation of the device within the NHS setting.

2.5 SAMPLE SIZE CALCULATION

We performed a series of sample size simulations based on baseline annual exacerbation frequencies of 2, 3 and 4 per patient, with estimated reductions (effect sizes) of 25%, 33% and 50%, with power to detect a difference at 80% and 90%. We then approached our Public and Patient Involvement group in the grant application to assess what a conservative but clinically meaningful reduction would mean for patients with severe asthma if this treatment was adopted in the NHS, and they agreed that a 25% reduction (equivalent to one less severe exacerbation every 2 years) was quite acceptable. This level of reduction was also consistent with that observed in previous trials of

severe asthma with effect sizes ranging from 21% to 63%, mean 41% (see Appendix G). Given that this was a pragmatic trial where we expected our intervention to be less effective than an efficacy trial, we deliberately chose a more conservative effect size of 25%.

Using the exacerbation frequency as the primary dependent variable, we considered whether the distribution of this count data was likely to approximate a Poisson or a negative binomial distribution. Previous trials have modelled analyses of exacerbation frequency by either using the Poisson approach (Pauwels et al 1997, Castro et al 2009, Hanania et al 2011, Humbert et al 2005, Bruselle et al 2012) or negative binomial (Bleecker et al 2016, Pavord et al 2012, Haldar et al 2009). Poisson is the traditional model favoured by the LASER trial statistical team, but this assumes the mean of the exacerbation frequency should approximate its variance. We considered aspects of the trial that would lead to the variance being greater than the mean i.e. "overdispersion". These factors included the within-participant clustering due multiple exacerbations, no limit on exacerbations that can be experienced, the duration of follow up constrained to 12 months, the effect size and how the event rate may change during the Trial, and how many baseline covariates that would require adjustment. In calculating the sample size, we selected the Poisson distribution after consideration of different factors but included an allowance of 20% for over-dispersion to reduce the effect of an unequal mean and variance. In so using a Poisson approach for sample size estimation, it was also agreed that the final fit of the count data would determine which model (Poisson, negative binomial or a mixed approach) would be appropriate for analyses of the primary outcome.

Settling on an estimated rate of 2 severe asthma exacerbations per participant over the 12-month period in the placebo group, we calculated that a minimum of 222 participants (111 per group) was required to provide 80% power (at 5% two-sided significance level) to detect that clinically meaningful 25% reduction in the average exacerbation rate in the group using the TLA device. This sample size was based on a Poisson regression model with the treatment group as the covariate a 10% overall dropout rate and an adjustment of 20% Poisson over-dispersion (Royston 2004).

2.6 PARTICIPANT SCREENING AND ENROLMENT

2.6.1 SCREENING VISIT (-2 WEEKS)

Informed Consent was sought for participation in the main trial as well as the qualitative focus group sessions at the Screening Visit. Informed Consent (Appendix C and Appendix D) preceded any study procedures (including tests to ascertain eligibility for trial inclusion), thus ensuring the individual had had an opportunity to fully discuss the Participant Information Sheet (PIS) (Appendix A and Appendix B) with the research team.

If the individual passed all inclusion and exclusion criteria pertinent to the Screening Visit (namely the baseline spirometry including reversibility test, skin prick test, blood test and ACQ score criteria described in Section 2.2.3), they were trained in use of the electronic PEF meter to measure morning

and evening PEF (prior to taking asthma medications) and completion of the Asthma Control Diary (ACD) for the 2-weeks prior to Randomisation Visit 2.

2.6.1.1 Extension of Screening Period

To continue to be deemed a potentially eligible trial participant, individuals needed to demonstrate acceptable compliance with the electronic PEF recordings and Asthma Control Diary (ACD) during the 2-week screening period. However, in the event of electronic PEF device malfunction or if, in the investigator's opinion, there were significant extenuating circumstances, the screening period was extended by up to a further 2 weeks. Participants experiencing a severe exacerbation during the screening period were no longer eligible but could be re-screened 2 weeks after returning to their maintenance asthma medications.

2.6.2 Randomisation Visit 2 (0 Months)

The following data collected during the screening period and at the Randomisation Visit (Study Visit 2) were used to assess whether the potential participant fulfilled the following remaining eligibility criteria (see Section 2.2.3 for full description of eligibility criteria):

- Demographics, asthma history and asthma review (see Section 2.10.1.1)
- Review of Asthma Control Diary (ACD), including electronic PEF recordings (see Section 2.10.2.1)
- Asthma Control Questionnaire (ACQ) score (see Section 2.10.1.4)

Those individuals who met these remaining eligibility criteria were confirmed as eligible for participation. The data used in the final eligibility assessment were supplemented by the following data in the Case Report Form (CRF) to act as baseline data (see Section 2.10.1 for descriptions of these measures):

- SNOT-22, AQLQ(S), EQ-5D-5L and WPAI(A)
- Fractional concentration of exhaled nitric oxide (F_ENO)
- Baseline spirometry after withholding bronchodilator (Pre-bronchodilator FEV_1)

Finally, the participant was then provided with the materials they required to measure and record the primary and secondary trial outcome data (see Sections 2.4.1 and 2.4.2. for outcome definitions, respectively), including a TLA diary for self-reported device usage (see Section 2.10.2.2), at least 3 Exacerbation Diaries (PED, see Section 2.10.2.3), and a 2-week Asthma Control Diary (ACD, including electronic PEF recordings – see Section 2.10.2.1) issued for completion in the 2 weeks prior to the 3-month follow-up visit.

2.7 RANDOMISATION

2.7.1 DEVICES

The trial statistician generated a list of LASER specific device numbers (L-numbers) coded against an X or a Y (i.e. active or placebo), which they sent in a password-protected electronic file to the following Airsonett® personnel only: Chief of Operations, the Director of R&D and the Director of QA. This list was generated using STATA version 13.1 command RALLOC. A total of 400 codes were generated in blocks of 20 (10 active and 10 placebo) in line with Airsonett® manufacturing the devices in blocks of 20.

The Airsonett® personnel with access to the list oversaw the manufacture of the active and placebo devices according to these L-numbers. Each device was labelled with both L-number and manufacturing serial number.

2.7.2 PARTICIPANTS AND MINIMISATION CRITERIA

Once the eligibility of an individual was confirmed at the Randomisation Visit, the trial team at the recruiting site contacted the Oxford Respiratory Trials Unit (ORTU) to arrange randomisation. Participants were randomised in a 1:1 ratio to receive either an active TLA device or a placebo device. Randomisation was undertaken centrally by Sealed Envelope™ using a validated computer randomisation program including a nondeterministic minimisation algorithm to ensure balanced allocation of participants across the two treatment groups for each 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 FEV_1 (>50% predicted yes/no), as these are key indicators of future exacerbation risk. This approach accounted for the characteristics of the participants who had been previously randomised when randomising each new participant. By trial end, 119 of the 240 participants were allocated an active device, and 121 were allocated a placebo device.

*(Participants previously known to the recruiting Centre were termed Prevalent participants, whereas participants not previously known to the recruiting Centre but maybe referred from another Centre or through a social media channel were termed Incident participants).

Once participant randomisation was complete, Sealed Envelope™ sent a secure e-mail to the local trial team to confirm randomisation and to provide the information required for implementation described in Section 2.8. Note the device allocation was embedded into the Sealed Envelope™ system.

2.8 IMPLEMENTATION

After randomisation of each new participant to the active or placebo treatment group, Sealed Envelope™ selected which device with the appropriate treatment would be received by each randomised participant. It then sent secure e-mail and SMS message to the local independent device distributors (Bishopsgate, UK-based logistics company which specialises in medical devices) with the following details: Participant trial number, allocated L-number (without X or Y designation so that allocated treatment arm remained concealed) and an exclusive link for the engineering team to log in to access the participant's contact details and address.

2.8.1 DEVICE INSTALLATION

The Bishopsgate engineering team contacted the participant within 72hrs of their Randomisation Visit to arrange device delivery and installation. The engineering team were trained with certificates of competency based on completion of a GCP training course on trial procedures, and they followed a standard device delivery, filter change and removal protocol developed by the Trial team. The agreement with Bishopsgate was that devices should be installed within 10 working days, excluding weekends and bank holidays. They left written instructions on device operation with the participant during the installation visit.

2.8.2 DEVICE MAINTENANCE

All devices require a filter change on a 6-monthly basis. The date for the filter change was automatically calculated from the date of randomisation. The Trial Manager informed Bishopsgate on a monthly basis which participant's devices required a filter change. Bishopsgate contacted the participant to arrange a convenient date and time for filter change.

2.8.3 TROUBLESHOOTING

Participants were asked to report problems with device function with their local site team as soon as possible. If required, arrangements were made for a Bishopsgate engineer to attend to replace a faulty device with an alternative device of the same allocation (active or placebo).

2.9 BLINDING

The methods described above for the manufacture of active and placebo devices, the allocation of participants to the two treatment arms and the implementation of device installation ensured that all participants, trial teams and members of the installation team were blinded to the trial treatments. This process ensured that everyone with the exception of the Trial statistician who generated the codes for the devices and the programmers at Sealed Envelope™ were blinded to the treatment allocation. The Airsonett® team were the only party to know the difference between the

active and placebo devices but they did not have access to any participant information or to device allocation in the UK.

2.10 STUDY ASSESSMENTS

This section describes all the data collected at the Study Visits, including those recorded between Study Visits:

Quantitative Data

- **Demographics, asthma history and asthma review**
- **Lung function measures**
  - Pre-bronchodilator FEV_1
  - Post-bronchodilator Reversibility Testing
  - Fractional concentration of exhaled Nitric Oxide
- **Allergy testing**
  - Skin Prick Test
  - Serum Specific IgE Testing
- **Participant questionnaires**
  - Asthma Control Questionnaire
  - Standardised Asthma Quality of Life Questionnaire (disease-specific quality of life)
  - EuroQol-5 Dimensions 5-levels (generic quality of life)
  - 22-item Sino-Nasal Outcome Test (rhinosinusitis health status)
  - Global Evaluation of Treatment Effect Questionnaire
  - Work Productivity and Activity Impairment Questionnaire
- **Pre-visit data collection**
  - Asthma Control Diary (ACD)
    - Peak Expiratory Flow (PEF) Rate
    - Symptom and Reliever Medication Use
  - TLA Diary
    - Device usage
    - Daily Corticosteroid dose
    - Reliever usage

Qualitative Data

- **Focus Groups**

This quantitative and qualitative data were used for one or more of the following six purposes:

P1. To inform eligibility of an individual to participate in the trial against the inclusion and exclusion criteria (see Section 2.2 for criteria)
P2. To build the primary outcome dataset (see Section 2.4.1 for Primary outcome definition)
P3. To build the secondary outcome datasets (see Section 2.4.2 for Secondary outcomes definitions)
P4. To create participant factor datasets used to control the primary and secondary outcome data against associations unrelated to the treatment
P5. To contribute to the baseline outcome datasets
P6. To build the supplementary variable datasets

The purpose of each type of data mentioned in this section is indicated by the above corresponding letters.

2.10.1 Quantitative data

2.10.1.1 Demographics, asthma history and asthma reviews

The following data were recorded about each participant on the CRF at the Randomisation Visit only:

- **Demographics**
  - Age **(P1, P4)**
  - Gender **(P4)**
  - Socio-economic class **(P4)**
  - Ethnicity **(P4)**
- **Asthma History**
  - Date of asthma diagnosis **(P1, P4)**
  - History of life threatening and near fatal asthma exacerbations (ITU admissions) **(P6)**
  - Number of severe asthma exacerbations in previous 12 months **(P1, P5)**
  - History of previous asthma treatment **(P1)**
  - History of atopy **(P1)**
  - Family history of asthma/atopy **(P6)**
  - Asthma triggers **(P1)**
  - Medical or surgical co-morbidities **(P1)**
  - Occupational history **(P1)**
  - Smoking history **(P1)**
  - Height (cm) / Weight (kg) for measuring predicted lung function **(P3)**

The following data were collected at each follow-up visit as well as at the Randomisation Visit and recorded by the attending clinician on the FU / CRF, respectively:

- **Asthma Review**

  - Current asthma symptoms and treatment **(P1, P3, P5)**
  - Current medications **(P1)**
  - History of severe asthma exacerbations since previous trial visit and current participant-reported clinical status (still in exacerbation or recovered) **(P2)**
  - Unscheduled asthma-related healthcare use **(P3)**
  - Work / study days lost as a result of asthma symptoms **(P3)**

2.10.1.2 LUNG FUNCTION MEASURES

The following indicators of lung function were collected at the Study Visits:

- **Pre-bronchodilator FEV_1 (P1, P3, P5)**

Spirometry was conducted at the Screening Visit, Randomisation Visit and 3, 6, 9 and 12-month Follow-up Visits to collect the following variables:

- FEV_1 (Litres)
- FVC (Litres)
- FEV_1/FVC ratio
- FEF_{25-75} (%)

FEV_1 and FVC were documented as both absolute values and as a percentage of the predicted value.

A spirometer conforming to ATS/ERS standards (Miller et al 2005) was used as specified by the manufacturer's instructions.

- **Reversibility Testing (P1, P3, P5)**

Post-bronchodilator FEV_1 (both percentage change and volume change) was measured at the Screening Visit and 12-month Follow-up Visit only.

Following ATS/ERS standards (Miller et al 2005,) post-bronchodilator FEV_1 was 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 was considered significant.

- **Fractional concentration of exhaled Nitric Oxide (P3, P5)**

F_ENO was measured before spirometry at the Randomisation Visit and 3, 6, 9 and 12-month Follow-up Visits. The measurements were made using a NIOX MINO® device (Aerocrine AB®, Solna, Sweden) as specified by the manufacturer's instructions and outlined in the ATS/ERS standards for the measurement of exhaled Nitric Oxide (ATS/ERS 2005).

2.10.1.3 ALLERGY TESTING

The following allergy tests were made during the Screening Visit to determine whether the allergy-related trial inclusion criteria were met:

- **Skin Prick Testing (P1)**

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 was performed on all subjects. This occurred during the Randomisation Visit instead of at the Screening Visit if antihistamine hold was required (see Appendix J). Skin prick testing was performed in accordance with the Practice Parameter released by the American Academy of Allergy, Asthma and Immunology (Bernstein et al 2008). A positive skin prick test reaction was measured as a wheal of at least 3mm in diameter greater than the negative control.

- **Serum Specific IgE Testing (P1)**

If skin prick testing was not available, a blood sample was taken 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 was considered to represent allergen sensitisation. Serum specific IgE testing could also have been used if there was uncertainty about a skin prick test result or there was a negative skin prick test result in the context of a patient on long term maintenance systemic corticosteroids.

2.10.1.4 PARTICIPANT QUESTIONNAIRES

- **Asthma Control Questionnaire (ACQ) (P3)**

The well-validated 7-item Asthma Control Questionnaire (ACQ) (Juniper et al 1999) was used to assess asthma control over the 7 days leading up to the Screening Visit, Randomisation Visit and 3, 6, 9 and 12-month Follow-up Visits. It was administered at the same time during each visit with the participant blind to the results of other tests.

The ACQ includes 5 symptom scores, the amount of daily rescue bronchodilator usage and a measure of airway calibre (FEV_1% 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. It has a validated minimal important difference of 0.5 to demonstrate clinical significance.

- **Standardised Asthma Quality of Life Questionnaire (AQLQ(S)) (P3)**

Asthma-specific quality of life was measured using the Standardised Asthma Quality of Life Questionnaire (AQLQ(S)) (Juniper et al 1993) at the Randomisation Visit and 3, 6, 9 and 12-month Follow-up Visits.

The AQLQ(S) consists of 32 questions within 4 domains: 1. symptoms, 2. activity limitation, 3. emotional function and 4. environmental stimuli, and it has strong measurement properties and a validated minimal important difference of 0.5 (Juniper et al 1994). 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(S) score is the mean of all 32 responses and the individual domain scores are the means of the items in those domains.

- **EuroQol-5 Dimensions 5-levels (EQ-5D-5L) (P3)**

Generic Health-Related Quality of Life (HRQoL) was measured using the EuroQol-5 Dimensions 5-levels (EQ-5D-5L) questionnaire at the Randomisation Visit and 3, 6, 9 and 12-month Follow-up Visits (EuroQol Group 2011).

The EQ-5D-5L is a standardised measure of health providing a simple generic measure of health for clinical and economic appraisal. Patients are asked to think about their health in the day they are completing the questionnaire and report on any problems (none, slight, moderate, severe and unable/extreme) on 5 attributes (mobility, self-care, usual activities, pain/discomfort and anxiety/depression).

In addition to the EQ-5D-5L score, the EQ Visual analogue scale (VAS) was also ascertained at each of these Visits. EQ-VAS was determined by asking the participants to indicate their health status on a 20 cm vertical scale with end points of 0 and 100 (VAS; 0=worst health you can imagine to 100=best health you can imagine) at each Visit.

EQ-5D-5L is the most widely used HRQoL measure in adults in the UK and has been shown to be a reliable and valid means of measuring quality of life in asthma patients (Pickard et al 2008).

- **22-item Sino-Nasal Outcome Test (SNOT-22) (P3)**

The 22-item Sino Nasal Outcome Test (SNOT-22) score is a well validated and sensitive measure of rhinosinusitis health status (Hopkins et al 2009) that was recorded at the Randomisation Visit and 3, 6, 9 and 12-month visits.

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). Participants were asked to rate the problems according to how they had been over the previous 2 weeks.

- **Work Productivity and Activity Impairment: Asthma version 2.0 (WPAI(A)) (P3)**

The WPAI(A) is a validated questionnaire tool for assessing work productivity and activity impairment that was completed by participants at the Randomisation Visit and at the 3, 6, 9 and 12-month visits.

This questionnaire comprises 6 questions addressing absenteeism, presenteeism (reduced effectiveness whilst working,) overall work productivity loss (absenteeism + presenteeism) and activity impairment (Reilly et al 1993). Participants were asked to count the number of hours they had missed from work because of problems associated with their asthma and the number of hours missed for other reasons (such as vacation, holidays, etc) over the past seven days. In addition, participants were also asked to report from a scale (1=asthma had no effect to 7=asthma completely prevented me) the impact of asthma on their work and on the ability to do regular daily activities.

WPAI(A) outcomes are measured as percentages and a higher percentage relates to greater impairment and reduced productivity. A modified WPAI(A) was used for student participants.

- **Global Evaluation of Treatment Effect (GETE) (P3)**

The Global Evaluation of Treatment Effect (GETE) questionnaire (Lloyd et al 2007) is a simple measure of perceived treatment effectiveness that was completed by participants and clinicians at the 12-month visit.

This questionnaire has been used in the evaluation of other treatments in patients with severe allergic (IgE mediated) asthma. For the purposes of the LASER trial, it required participants and physicians 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).

2.10.2 Pre-visit data collection

2.10.2.1 Asthma Control Diary (ACD)

Participants were issued with a validated Asthma Control Diary (ACD) (Juniper et al 2000) at the Screening Visit, Randomisation Visit and 3, 6 and 9-month visits to record data for the 2-weeks leading up to their subsequent visit. Towards the end of the trial, a text reminder system was set up

to remind participants when to start their ACD and to remind them of the date of their follow-up visit.

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

- **Peak Expiratory Flow (PEF) Rate**

During the trial, participants performed 3 morning PEF measurements using a hand-held device supplied by the trial team, and recorded these measurements in the ACD.

During the screening period, participants also performed 3 evening PEF measurements to assess variability as part of eligibility assessment. This additional PEF data was stored on the PEF device and downloaded at the Randomisation Visit.

- **Symptom and Reliever Medication Use**

The ACD 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).

2.10.2.2 TLA Diary

Participants were issued with a TLA diary (Appendix K) at the Randomisation Visit to record the following data on a daily basis:

- **Use of the TLA device (hours), i.e. participant-reported treatment adherence**
- **Reliever used (number of times)**
- **Dose of corticosteroids (mgs)**

2.10.2.3 Exacerbation Diary (PED) and Exacerbation Review Forms (REV)

Participants were asked to start an exacerbation diary (PED) (Appendix L) when exceeding the 'exacerbation-dose' threshold of systemic corticosteroids individually defined for each participant during Randomisation Visit 2. The PED recorded the following during exacerbations for a period of 7 days:

- **Morning PEF (L/min) (recorded using the trial-supplied electronic PEF device)**
- **Steroid Dose (mgs)**
- **Reliever use (number of times)**
- **Nocturnal wakening (yes/no)**

In addition to completing the PED, participants were asked to report severe exacerbations to their local site trial team as soon as possible after onset via a dedicated telephone line or a secure NHS e-

mail account. Wherever possible, participants were asked to attend an Exacerbation Review session with their local trial team within 72 hours to corroborate the exacerbation, at which the local trial team completed the Exacerbation Review Form (REV) (Appendix M). The following information were captured on the REV:

- **Onset of symptoms (date)**
- **Steroid Dose (mgs)**
- **Corroboration of exacerbation dose of corticosteroid (at least 30mg for 3 days)**
- **Change in symptoms vs. baseline**
- **Change in daily reliever use vs. baseline**

If participants were not able to attend an Exacerbation Review, a review of the exacerbation occurred by telephone and a REV was still completed. If a telephone review was not possible either, a REV was completed at the next Follow-up Visit. The nature of the review (face-to-face or telephone) was recorded on the REV.

In all cases, the participant's PED was collected at their next Follow-up Visit and used to corroborate other sources of primary outcome data.

2.10.2.4 Follow-up Visit Forms

A regular 3-monthly Follow-up Visit Form (FU) was completed by the Trial site team at each Follow-up Visit (at 3, 6, 9 and 12 months), prompting discussion with the participant about key issues related to the past 3 months. This included numbers of exacerbations, a review of the TLA diary, medication use, work and study days lost, reported device use, completion of Trial questionnaires, F_ENO and spirometry. These data were used to corroborate other sources of primary and secondary outcome data during statistical analysis.

2.10.3 Qualitative data

2.10.3.1 Sampling and Recruitment

All 240 LASER trial participants were invited to participate in the qualitative study and were given written information about the qualitative component of the trial as a separate Participant Information Sheet (Appendix B).

Informed consent for participation in the qualitative study was sought at the LASER Trial Screening Visit (Appendix D).

Not all participants who consented to taking part in the focus group sessions were selected: 5-10 participants were selected for each of three focus group sessions on the basis that they best reflected multiple variation (including balance of gender, age and ethnicity).

2.10.3.2 FOCUS GROUPS

A focus group is an interview technique where a group of individuals are encouraged to debate and discuss around specific topic areas. The rationale for choosing focus group discussions during the LASER trial was to stimulate alternative views and experiences, evaluate the process and assess the feasibility of the intervention.

28 participants were invited to attend focus group sessions based on the fact that they had completed at least 9 months of the trial and had consented to attend local focus group sessions when asked at the start of the trial. 20 of these 28 participants agreed to attend a session and were sent invitation letters to attend one of three focus group sessions hosted by the Portsmouth site during January 2016. The three sessions were held on separate dates at different times of the day including an evening focus group in order to provide choice to those invited to attend and maximise attendance. The venue chosen was a non-NHS, non-trial centre, within an easily accessible location with on-site parking, namely, the Premier Inn Hotel in Port Solent.

Acceptance of the invitations covered consent for the use of verbatim quotations and assurance that the information that a participant provided would be kept strictly in confidence and anonymised.

The focus groups were led by a senior qualitative researcher from the University of Portsmouth (Dr Ann Dewey); with a Senior Medical Research Fellow (Dr Will Storrar) attending as facilitator and note keeper.

Focus Group One was held on 21st January 2016 at 1800hrs. Five participants agreed to attend but only one participant attended. It was agreed to conduct a one-to-one interview with this participant, following the focus group topic guide.

Focus Group Two was held on 26th January 2016 at 1000hrs. Seven participants agreed to attend but only three participants attended on the day.

Focus Group Three was held on 28th January 2016 at 1400hrs. Eight participants agreed to attend but only six attended on the day.

In total, ten participants took part in the focus group sessions. These ten participants represented both satisfied and non-satisfied participants (determined from a combination of device reported usage and participant-reported device usage) and there were slightly more females than males represented (Females 7; Males 3).

At the beginning of each focus group discussion, the facilitator checked that participants were aware of the purpose of the focus group discussion, likely topics to be discussed, and the right to leave, at any time, without giving a reason to do so. All participants were asked to respect others views, and to take turns in speaking to aid the recording of the discussions.

The topics were based on key themes identified during qualitative telephone interviews conducted during the pilot phase of the LASER trial (Appendix K – *LASER Focus Group Interview Schedule*). Free discussion of experience and ideas was encouraged throughout.

The focus groups were audio recorded and lasted between 60 and 90 minutes. Afterwards, audio recordings were transcribed verbatim by the 'Way With Words' secure online transcription service. Participants were offered tea or coffee, with biscuits, with water available throughout.

2.11 STATISTICAL METHODS

All statistical analyses were undertaken using a validated statistical package: STATA/IC version 14.2 (StataCorp LLC www.stata.com). The results are presented as comparative summary statistics (difference in response rate or means) with 95% confidence intervals, in accordance with the CONSORT 2010 statements (Schulz 2010). All the tests are done at a 5% two-sided significance level.

2.11.1. DEFINING POPULATIONS FOR DATA ANALYSIS

2.11.1.1 PRIMARY STATISTICAL ANALYSIS

The primary statistical analysis was based on the **intent-to-treat (ITT) population**, which is defined as all participants included and analysed according to their allocated treatment group irrespective of the treatment received. Note that in the primary analysis, the five participants who were randomized and withdrew consent to allow data usage were still included, with data set to missing and assumed no severe exacerbations. All other participant data deemed to be ineligible post-randomisation or associated with protocol violations was also included in these primary outcome data.

- **Per-protocol population**

As the ITT population but excluding:

  - participants who did not receive a device
  - participants who withdrew consent for data use

- **Minimum data population**

All participants who have at least 90 days of steroid dose information reported (in TLA Diary or exacerbation diary (PED)) or have reported at least one PED. This requirement counted the assumed doses on the TLA Diary, and PEDs where the dosage was left blank.

2.11.1.2 SECONDARY STATISTICAL ANALYSIS

Analysis of secondary outcomes was carried out on a variable-by-variable complete case basis i.e. participants were only included in each individual secondary outcome analysis if all data relevant to that specific analysis were available, with no requirement on their remaining (non-relevant) data. Secondary outcomes with insufficient data were not analysed.

2.11.2 ANALYSIS OF PRIMARY ENDPOINT

2.11.2.1 DEFINITIONS

Primary end-point definition = rate of severe exacerbations in a 12-month period.

Severe exacerbation (defined in accordance with ATS/ERS guidelines (Reddel et al 2009)) = 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 are treated as separate severe exacerbations.

A post-hoc analysis included the use of a worsening of asthma requiring systemic corticosteroids, ≥10mg prednisolone or equivalent daily for 3 or more days with exacerbations separated by ≥7 days treated as separate exacerbations.

2.11.2.2 DATA COLLECTION

In an attempt to not miss any exacerbations, the primary outcome was collected from several different sources, which are listed in **Table 2.3**, along with a description of the source of these data: patient or trial site.

Some participants provided detailed information including dates and doses of corticosteroids, but others just provided number of severe exacerbations with no corroboration regarding the severity and duration of the exacerbation in relation to the definition described above.

It was decided that the most appropriate data to use for the primary outcome was the dated information as this was the most accurate and would enable duplicate reporting to be removed and the definition to be applied. The primary outcome for this study was therefore determined from the dated primary outcome data only.

Table 2.3 Sources of primary outcome

Source	Abbreviation	Timing / Description	Source
Dated Severe Exacerbations			
TLA Diary	TLA	Daily	Participant
Exacerbation Diary	PED	As severe exacerbation happens	Participant
Exacerbation Review Form	REV	After reported severe exacerbation	Site
Adverse Event / Serious Adverse Event	SAE	Ad hoc	Site
Hospitalisations recorded on Follow-up Visit form	HOSP	Every 3 months, with dates obtained retrospectively from site of hospitalisation	Information provided by participant and recorded and validated by site

Primary Outcome	Dated Severe exacerbations	Combination of all the above, with duplicates removed	
Undated severe exacerbations			
Number of severe exacerbations recorded on Follow-up Visit form	FU	Every 3 months	Information provided by patient and recorded by site

2.11.2.3 STATISTICAL MODEL

The primary efficacy end point, which is the rate of severe exacerbations over the 12-month period, was analysed using the negative binomial model. The only adjustment made to the model was the minimisation factors used in the random assignment. In theory, randomisation provides balance for the known and unknown factors, and given the large sample size in this trial, it was expected that overall balance would be achieved without additional adjustment for time or device usage. The Minimisation factors used in the models were prevalent vs. incident cases, exacerbation frequency in the previous 12 months (2, 3, ≥3), use of oral corticosteroids (yes/no) and pre-bronchodilator FEV_1 (>50% predicted yes/no). Recruiting Centre was included in the models. The negative binomial model was chosen over the originally planned Poisson model because it was more flexible and gave a better fit to the overall blinded data.

In the current data, there are approximately 60 cases where the participant reported a severe exacerbation in the PED but there was no report or no data in the daily diary. There are also approximately 50 severe exacerbations reported by the research team without corresponding daily diary entries or PED report. Thus, there are approximately 110 severe exacerbations without documentation of how long the participants were being observed. Therefore, as it could not be ascertained which days participants were actively reporting severe exacerbations if they did not complete the daily diary, it was decided that for dated severe exacerbations the observation period would extend from randomisation to 365 days after randomisation for the primary analysis. By taking a full year as the denominator for all participants, we essentially assumed that all days were at risk as we did not have exact days at risk for the model. This method most likely leads to an underestimation of the rate of events, however it was deemed the best approach to handling the problems of large amounts of missing diary data, and so supporting the use a negative binomial approach. When using undated data from the FU, all data up to and including the 12-month Follow-up Visit was used.

2.11.2.4 SENSITIVITY ANALYSES

The following individual sensitivity analyses were carried out to test the robustness of the primary outcome to the missing data:

1) Participant population definition

The primary analysis was repeated with the ITT participant population replaced by the Per-protocol population (see Section 2.11.1 for descriptions), meaning that participants who did not receive a device and the five who withdrew their consent for their data to be used in the analyses were excluded from the primary analysis. All other protocol deviations were deemed as minor.

2) Best and Worst Case

The primary analysis was repeated but with the following best and worst case severe exacerbation substitutions for those participants who did not contribute a minimum amount of data (see Section 2.11.1 for definition):

Modified best and worst case

- Worst imputed case
  Placebo arm with missing data: best possible outcome is assumed.
  Active arm with missing data: worst possible outcome is assumed.

- Best imputed case
  Placebo arm with missing data: worst possible outcome is assumed.
  Active arm with missing data: best possible outcome is assumed.

Usually a best and worst case scenario would use the maximum and minimum number of observed attacks. We instead used the 90th and 10th percentile to avoid using extreme values and so refer to our best and worst case analysis as modified best and worst case analysis. This should put a reasonable bound on the assumptions made about missing data and how these affect the outcome of the trial. It is believed most other reasonable attempts at estimating the missing data will fall between these two extreme bounds, and this will aid correct interpretation of the results.

2.11.3 ANALYSIS OF SECONDARY ENDPOINTS

Complete case analysis (or, in the case where we were looking over multiple time points, cases with data from at least one Follow-up Visit) was carried out for all secondary outcomes, i.e. only available data was analysed with no missing data imputation. Missing data is reported.

A multilevel mixed-effects linear regression which includes the treatment term, a time point term, an interaction term of treatment arm and time point, the baseline measure, and the minimisation

factors, and that is adjusted for repeated observations on participants, was used to analyse the continuous secondary outcomes. The minimisation factors for the secondary outcomes were prevalent vs. incident cases, exacerbation frequency in the previous 12 months (2, 3, ≥3), use of oral corticosteroids (yes/no) and pre-bronchodilator FEV_1 (>50% predicted yes/no).

For continuous variables with only baseline and 12 months data available, only the minimisation factors and the baseline variable were included in the mixed-effects model. Where sufficient data for analysis was not available only descriptive statistics are reported.

2.11.4 Qualitative data analysis

Focus Groups were digitally recorded, transcribed verbatim and entered into NVivo 8, a qualitative software package for systematic and transparent data management. An identification using a pseudonym was assigned to each participant at recruitment. After tape recordings had been transcribed, the pseudonym was used to refer to individuals and no "real" names were included in any reports to maintain participant anonymity. Care was taken to always ensure any direct quotes used in study reports or papers to illustrate the findings were not directly attributable to individuals.

We used Framework Analysis, a three-stage analytic process, to analyse the qualitative data. This Analysis method involves identifying initial themes by indexing the content of the data and using these themes to guide the formation of a framework within which transcribed material is synthesised (Spencer et al 2013). Key categories are then identified to help describe the data.

The two researchers who had collected the qualitative data independently coded it all. They then compared findings and scrutinised the framework matrix to see if there was agreement with the categories generated. In the case of disagreement, a solution was sought to clarify the meaning of a code/theme developed until mutual consent was reached. The aim of this stage was to attempt to enhance the validity of the development of the conceptual framework and to guard against researcher bias. Following analysis of all focus groups, it was observed that data saturation had been achieved as no new themes were emerging from the participants.

Finally, the researchers explored patterns of association between the categories and attempted to explain why those patterns occurred.

2.12 Ethical Considerations

The LASER Trial protocol and all patient facing documents were submitted for review by the NRES South Central (Berkshire) Committee on 6th February 2014. The ethics committee met to consider the ethical implications of the trial on 18th February 2014. The Trial Chief Investigator and Trial Coordinator attended to answer questions from the ethics committee.

The primary issue of concern raised by the ethics committee was the risk to participants of being in the placebo arm of the trial. It was explained that unfortunately there was no suitable alternative comparator to the placebo device. Alternative treatment options for these patients including Bronchial Thermoplasty and the anti-IgE treatment Omalizumab vary significantly in indication, use and delivery. Omalizumab is only indicated in patients requiring maintenance oral corticosteroids for the treatment of asthma or who require 4 or more courses of oral corticosteroids to treat asthma exacerbations in a 12-month period. Bronchial Thermoplasty excludes patients with more severe lung function deficits who would not be able to tolerate the bronchoscopy procedure, requires skilled operatives and is only available in a small number of centres. A placebo comparator was hence chosen in the absence of a practical, directly comparable alternative.

Following the Declaration of Helsinki and CIOMS guideline statements (World Medical Association 2013) (CIOMS 2002) on the use of placebo controls in RCTs, it was felt that the use of a placebo was necessary to determine the efficacy of the treatment and that the participants receiving placebo would not be subjected to any increased risk of serious or irreversible harm.

The committee questioned the length of the trial treatment period. It was explained that the trial treatment period of 12 months was required to ensure that the seasonal variability in asthma control and symptoms was taken into account for all participants.

It was explained that the risk of being in the placebo arm of the trial for the 12-month trial period was being offset by the offer of 4 years of treatment with an active treatment device in the post-trial provision period. The device manufacturer, Airsonett®, had committed to providing to all participants who had completed at least 6 months of follow-up in the trial, the use of an active treatment device including servicing and filters changes for a 4-year period. The question was raised, what would happen after this 4-year period if participants had responded to the treatment. It was explained that by this time, there would be evidence either for or against whether there was a beneficial treatment effect in this patient group and that if so the treatment would be validated and available as a treatment within normal NHS provision.

The ethics committee questioned whether there was any risk that removal of the filter from the placebo device might result in increased delivery of allergens to the participants in the placebo arm of the trial, increasing their allergen exposure. It was explained that the filter was bypassed in the placebo device and that because there was no cooling of the air or laminar flow, the air delivered to the participant was no different to the ambient air in the bedroom environment. Although no particulate counts were being measured during the trial, each device was validated and tested before leaving the factory in Sweden for quality control purposes. In the 4A's trial where a similar placebo device was used, particulate counting was measured to ensure that there was no risk of increased allergen exposure in the placebo group.

The ethics committee asked about the cost to participants of running the treatment device. It was explained that the device uses an equivalent amount of electricity as a 60W light bulb and that the cost of electricity would be reimbursed to participants on a pro-rata basis during the trial follow-up period. It was agreed that this would be explained in the Participant Information Sheet.

The ethics committee were interested to understand about the noise level of the treatment device. It was explained that the measured noise level of the treatment device is 38dB and that this is equivalent to a quiet whisper or similar to an air conditioning unit. The committee asked whether this might be a barrier to device use. It was explained that in previous trials of the treatment device, very few participants had withdrawn as a consequence of the device noise. It was agreed that the noise level of the treatment device would be included in the Participant Information Sheet. It was also explained that the qualitative interviews would explore barriers to use of the treatment device and that we would specifically ask about tolerability of the noise level during these interviews.

The impact of the treatment on trial participant's partners was raised as a concern. The ethics committee asked whether the device would have any impact on participant's partners as they would also have to accept the installation of the device in the bedroom. It was agreed that this was an important consideration and that this was being addressed through invitation to participate in qualitative interviews conducted during the pilot phase of the trial. The purpose of these interviews was to determine the impact of the treatment, if any, on participant's bed-sharing partners.

The ethics committee asked about holiday periods and inclusion of participants who work away from home during the week and whether this would impact on their participation and the results. It was explained that this was a pragmatic trial and that we wanted the results to reflect real-world use of the treatment device and that this meant that we would have to accept that participants would not be able to use the device every night during the 12 month follow up period. It was explained that the trial eligibility criteria required participants to use the device on average 5 out of every 7 nights. Holiday periods were also acceptable. Use of the device was captured in the daily completion of the TLA-diary which specifically asked participants whether the treatment device had been used and for how many hours.

The committee queried whether it was possible to use a fan or air-conditioning unit in the same room that the device was installed and whether it was possible to have a window open in the room and the impact that this might have on the function of the device. It was explained that the function of the device would only be compromised if there was a significant cross draught that might interrupt the laminar flow of air delivered by the treatment device. As long as this could be avoided by ensuring that the fan or air-conditioning unit were not directed at the treatment device then there was no reason why they could not be used. Similarly, there was no reason why a window could not be opened as long as it did not result in a cross-draught that might interrupt the laminar airflow.

The ethics committee were advised that we wanted the trial to reflect real-world use of the device and that participants would be encouraged to continue 'life as usual' whilst using the device.

The ethics committee were satisfied with the responses to their questions and a favourable opinion for the trial was received on the 26th February 2014.

CHAPTER 3 RECRUITMENT

3.1 PARTICIPANTS

The LASER Trial opened to recruitment at Portsmouth Hospital on 7th May 2014 with the first participant randomised to receive an active or placebo treatment device on 25th May 2014 and the last participant recruited in January 2016. In total 545 participants were identified against the eligibility criteria for the trial during this period. 56 of these participants were later excluded with a total of 489 being approached for consent. 100 participants either refused consent or were excluded with a total of 389 being consented. Of these 389, 149 participants failed the screening phase. A total of 240 participants met all of the eligibility requirements and were randomised to receive either an active or placebo treatment device. These recruitment numbers are presented in **Figure 3.1**.

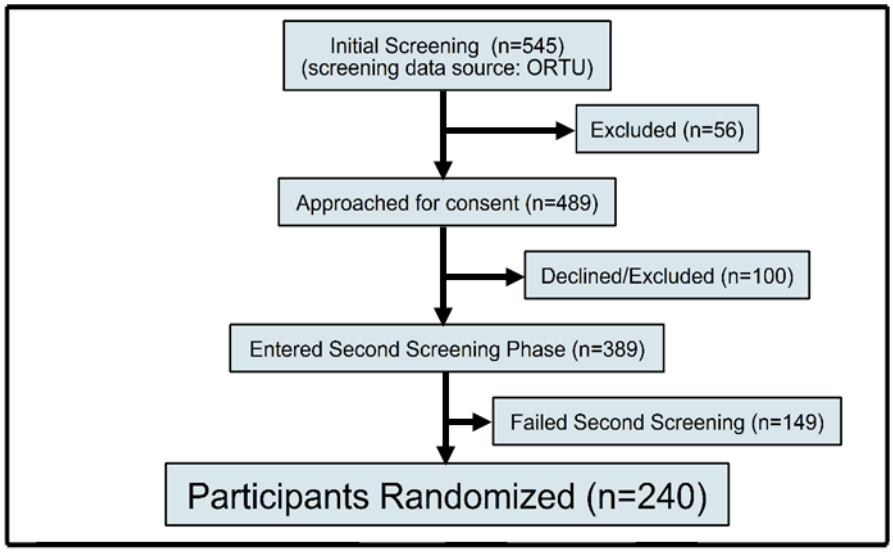


Figure 3.1 Participant recruitment

3.2 RECRUITMENT TARGETS

During the grant application process the NIHR-HTA requested an ambitious recruitment plan with an expectation of meeting the 222 participant target over an 18 month recruitment period (**Figure 3.2**). This recruitment plan was based on the large cohorts of asthma patients (prevalent cases) at the 4 lead recruiting centres, Portsmouth, Southampton, Leicester and Birmingham-Heartlands. Each of these centres has experience of recruiting patients to clinical research trials in asthma. It was expected that recruitment would be front loaded with a tail off towards the end of the trial (**Table 3.1**).

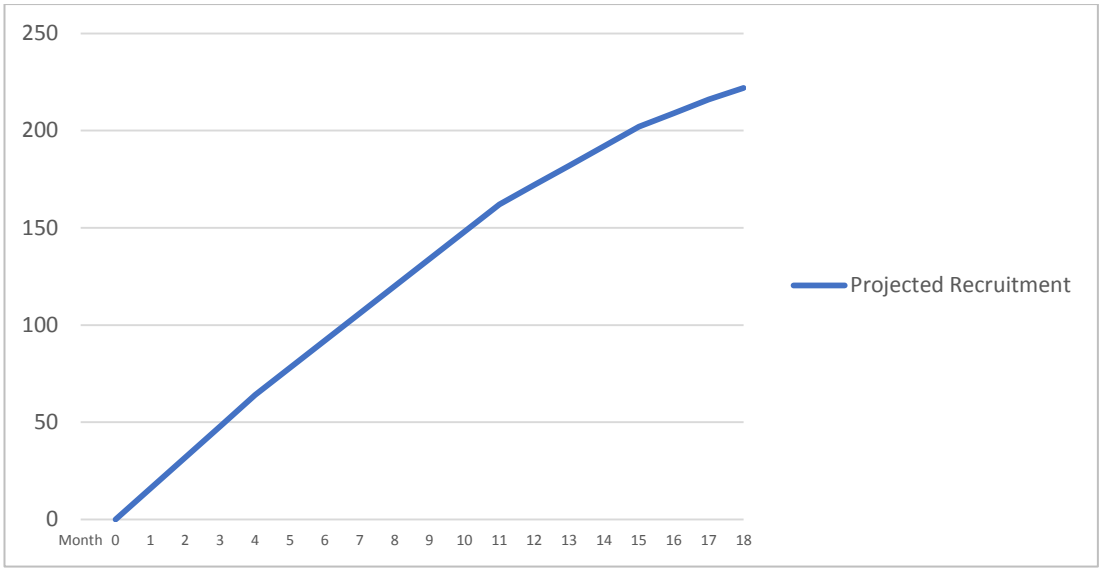


Figure 3.2 HTA Projected recruitment

Table 3.1 Monthly recruitment targets

Month	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**
Recruitment Target (n)	16	16	16	16	14	14	14	14	14	14	14	10	10	10	10	7	7	6

Unfortunately in the early stages of the trial it became apparent that the projected recruitment targets set out by the NIHR-HTA were not being met (**Figure 3.3**) and that we would need to take action to improve recruitment to the trial to ensure that the trial recruited to time and target without incurring additional costs.

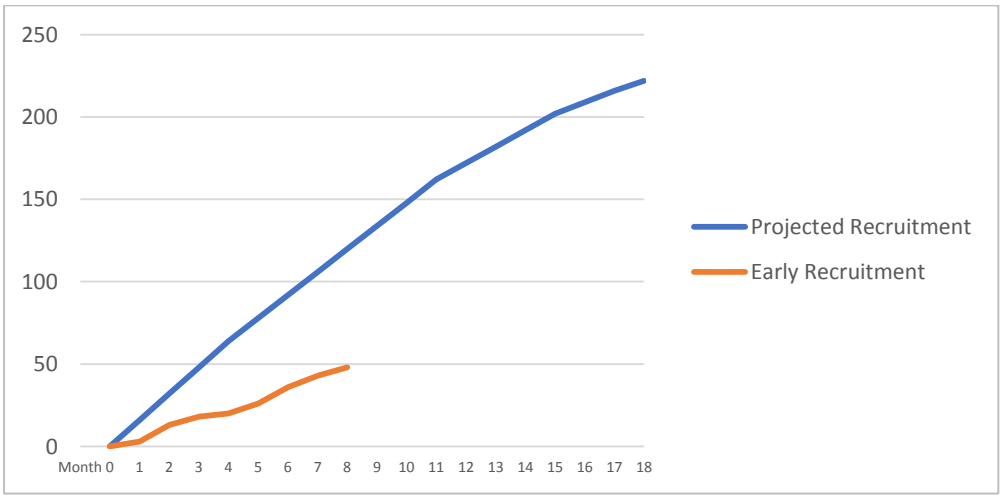


Fig 3.3 Early trial recruitment

This experience is not unique to the LASER trial; A review of recruitment data of a cohort of 151 RCTs funded by the NIHR-HTA Programme between 2004 and 2016 found that final recruitment sample size was only achieved in 85/151 studies (56%). (Walters et al. 2017).

Understandably the slower than expected early recruitment rate raised concern at the NIHR that the LASER trial might not reach its sample size or that there might be significant delays in reaching the recruitment target and subsequent publication of results.

The NIHR-HTA set a revised recruitment trajectory **(Figure 3.4).**

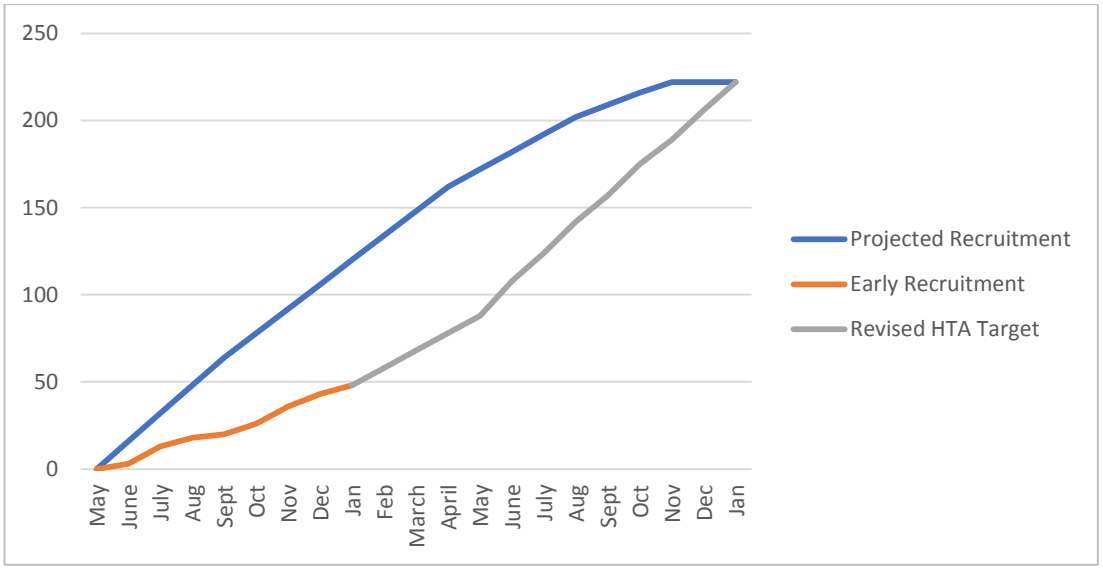


Figure 3.4 Revised recruitment trajectory

Having been set this challenge, the trial team identified a number of factors that might have contributed to the slower than expected early recruitment rate (Section 3.2.1) and put in place a number of remedial actions in order that the trial succeed in recruiting to the previously agreed time and target (Section 3.2.2).

3.2.1 Factors Contributing to Early Recruitment Failure

3.2.1.1 Delays in opening recruiting centres

There were significant delays in opening the initial 4 recruiting centres owing to unexpected delays in Research and Development department approval processes.

3.2.1.2 Smaller than expected pool of eligible participants

Thorough feasibility assessments were conducted at the 4 lead trial centres, Portsmouth, Southampton, Leicester and Birmingham-Heartlands during the grant application process. It was thought that we would be able to recruit the 222 participants from existing clinic cohorts at these 4

sites. When sites were opened it became apparent that the pool of eligible participants was smaller than had been expected. This is thought to be due to a number of contributory factors including:

Change in NICE recommendations for Omalizumab

After the trial began, NICE re-appraised their Technology Appraisal Guidance for Omalizumab, a drug manufactured by Novartis which is a costly injectable anti-IgE therapy, delivered from Centres with asthma specialists, and a treatment option that competes directly with the TLA device being tested in this Trial. In the 2007 guidance, the NICE recommendation included confirmation of IgE mediated allergy to a perennial allergen by clinical history and allergy skin testing, and with either two or more severe exacerbations of asthma requiring hospital admission within the previous year, or three or more severe exacerbations of asthma within the previous year, at least one of which required admission to hospital, and a further two which required treatment or monitoring in excess of the patient's usual regimen, in an accident and emergency unit.

The revised guidance broadened the inclusion criteria to include any patient who needed continuous or frequent treatment with oral corticosteroids (defined as at least 4 courses in the last year).

This expanded the population of patients who might be eligible for Omalizumab (no requirement to attend hospital or Emergency Departments and everyone on oral corticosteroids for asthma, irrespective of their prior exacerbation history). This change in NICE guidance had a negative impact on LASER Trial recruitment as it dramatically shrunk the anticipated 'prevalent' population of severe asthma patients previously identified by recruiting centres when performing our extensive feasibility assessments and recruitment projections.

Omalizumab Treatment Pathway

The change in licensed indication for Omalizumab led to considerable variation among Centres regarding the treatment option offered to patients. Several of our recruiting centres elected to offer patients Omalizumab therapy prior to being considered for the LASER Trial, even though they potentially met the eligibility for both treatments; some specialists were concerned that half of patients may be randomised to placebo in this Trial, and therefore could still remain potentially uncontrolled.

Our eligibility criteria allowed participants with severe allergic asthma to be recruited who had failed or only partially responded to Omalizumab therapy after a wash-out period of 120 days. Even then a 'trial' of Omalizumab treatment involves 2 weekly injections for 16 weeks before a patient is deemed to have responded or failed treatment. Thus, any potential participant who was first offered Omalizumab in preference to the LASER Trial device would test Omalizumab for 16 weeks (4 months) and then could not then be screened for another 3 months, delaying recruitment to the LASER trial even further.

Competition with other Commercial Research Trials

There has been a plethora of monoclonal antibody treatments for severe asthma in the last 3 years, sponsored by the pharmaceutical industry, and facilitated by all local Clinical Research Networks (CRNs) through their commercial portfolio to encourage Centres to participate in more commercial trials. The 30-day metrics of the CRNs ensures that Centres are incentivised and performance managed to recruit patients into all portfolio trials, including those that were competing with the LASER Trial. Naturally, nearly all of our Centres were approached to participate in the trials with significant variation in Centres signing up to such Trials, and in some cases, recruiting to them in preference to the LASER Trial.

NHS England Service Specifications for Severe Asthma Centres

In 2013, NHS England controversially approved the service specification for a limited number of Centres to be designated as Specialist Asthma Centres (SACs) (Birmingham, Brompton, Leicester and Manchester being approved at the time of commencement of the LASER Trial). Discussions continue to take place to revise the designation and the numbers of SACs. One criterion for specialist status had been the introduction of 'Bronchial Thermoplasty' (BT) as a new treatment option in severe asthma, with a requirement that each SAC perform 10 procedures per year to maintain status, and those aspiring to become a SAC required to perform a similar number over a 12-month period. Given the political incentives, potential participants eligible for LASER trial were, in some instances, considered for BT in preference to the LASER trial in order to meet the politico-clinical targets set by the service specification.

3.2.1.6 Higher than expected screen failure rate

The number of participants requiring active screening to the point of consenting was not known, and consequently recruiting centres had been unaware of the numbers of potential participants that needed to be screened over any given period of time to ensure sufficient numbers of patients would meet randomisation criteria. Based on our estimates we anticipated that 2 out of every 3 participants screened would progress on to randomisation.

Due to the patient population being assessed, a number of potential participants with poorly controlled asthma who met all of the eligibility criteria were unable to achieve the 6-week period of stable disease control required before randomisation without experiencing an exacerbation. (4 weeks stability prior to screening and 2-weeks stability during the screening period).

3.2.1.7 Resource problems

Despite the Trial being on the CRN portfolio, there were several instances of CRNs not being able to support sites with clinical staff due to lack of funding which required transfer of potential participants to other Centres. Other Centres similarly completed feasibility but did were unable to open for recruitment due to staff shortages.

3.2.2 Strategies to Improve Recruitment

3.2.2.1 Increased Number of Recruiting Centres

We recognised that we would need to open additional recruiting centres in order to meet our recruitment target. We identified an additional 21 recruiting centres with experience of recruiting patients to asthma trials and conducted feasibility assessments, eventually activating an additional 10 sites during the trial recruitment period (See **Table 2.2** for activation dates).

3.2.2.2 Trial Protocol Amendments

3 major amendments were made to the trial protocol in an attempt to improve recruitment. It was important that these amendments were implemented without impacting on the validity of the trial results. All protocol amendments were approved by the Trial Steering Committee (TSC) and subsequently by the trial Research Ethics Committee (REC).

Definition of Severe Asthma

The LASER trial sought to include participants with severe asthma. For the purposes of the LASER trial this was initially defined in the protocol as a requirement for treatment with high dose ICS or treatment with maintenance oral corticosteroids. The protocol definition of high dose ICS was >1000mcg BDP or equivalent ICS.

Setting the protocol threshold for trial participation at >1000mcg BDP equivalent meant that a large number of patients who were established on the commonly prescribed dose of 1000mcg BDP equivalent (e.g Symbicort 200 2puffs bd or Fostair 100 2 puffs bd) were excluded despite meeting all other protocol requirements for trial inclusion.

We wished to be as pragmatic as possible with the trial definition of severe asthma to reduce ambiguity.

The definition of 'severe' or 'difficult' asthma varies between different internationally recognised guidelines for managing asthma:

- **BTS/SIGN** define severe asthma as persistent symptoms and/or frequent exacerbations despite treatment at Step 4 or Step 5. BTS Step 4 includes patients on >800-2000mcg BDP equivalent.

- **GINA** recognises severe asthma as asthma that requires Step 4 or Step 5 treatment to maintain symptom control. GINA Step 4 includes patients on Medium dose ICS (500-1000mcg BDP equivalent) and High dose ICS (>1000mcg BDP equivalent).

- **NICE** recognises difficult asthma as asthma with symptoms despite treatment with step 4 or step 5 of the BTS/SIGN guideline plus one of the following:
    - An event of acute severe asthma which is life threatening, requiring invasive ventilation within the last 10 years,
    - Requirement for maintenance oral steroids for at least 6 months at a dose ≥7.5mg Prednisolone per day or a daily dose equivalent of this calculated over 12 months,
    - 2 hospitalisations within the last 12 months in patients taking and adherent to high dose inhaled steroids (≥1000mcg BDP or equivalent)
    - Fixed airflow obstruction with a post-bronchodilator FEV_1 of less than 70% of predicted.

Following discussion with the TSC it was agreed that the protocol requirement for high dose ICS should be reduced to include participants on ≥1000mcg BDP equivalent. This remained consistent with the BTS/SIGN, GINA and NICE definitions of severe or difficult asthma and remained inclusive of participants who would be clinically recognised as having severe asthma.

Reduced Length of Pre-Screening Stability

In order to reduce the 'screen failure' rate in those patients who had such poorly controlled asthma that they were unable to meet the requirement for 4 weeks of stable asthma treatment prior to entering the 2-week screening period for the trial, the stability period required prior to screening was reduced from 4 weeks to 2 weeks **(Figure 3.5).**

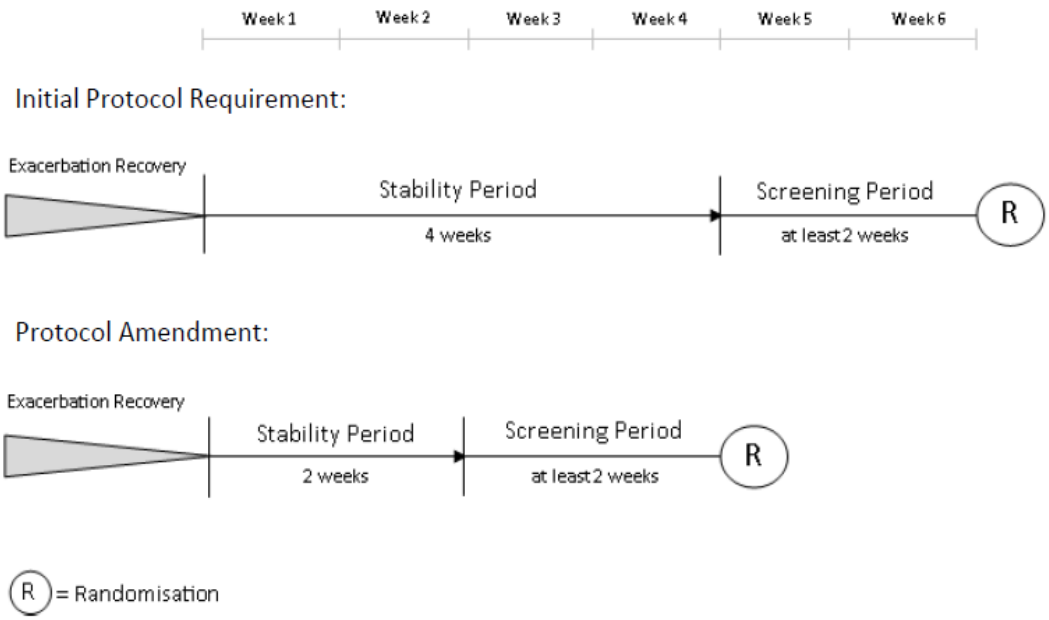


Figure 3.5 Reduced length of pre-screening stability.

Reduced lower age limit for participation

After consultation with the Trial Steering Committee it was agreed that the lower age limit for participation in the trial could be lowered to 16 years of age having previously been set at 18 years of age.

3.2.2.3 Increased engagement with trial centres

Investigator Meetings

3 investigator meetings were held during the trial recruitment period. The first meeting was held in Portsmouth with subsequent meetings being held in a central, more accessible location, the Marriott Hotel, Leicester. Members of the trial teams from all 14 centres were invited to attend to learn about trial progress and share their experiences.

These meetings were highly valued by site teams and allowed free and open discussion about recruitment challenges and strategies to improve recruitment rates.

Weekly Newsletter

Each week after the Trial Management Group (TMG) meeting, a newsletter was circulated to the trial teams at each recruiting centre with updates and information about the trial. Each week the newsletter included a 'Tip of the Week' to keep sites interested and engaged and focussed on recruitment targets.

Recruitmentometer

A 'Recruitmentometer' designed as a mock-up of a peak flow meter was added to the trial website homepage to display progress against the trial recruitment target. This gave trial teams real time updates of recruitment progress.

Incentivisation

As a means of incentivising trial teams to recruit patients to the LASER trial, an iPad was offered as a reward for the site with the best recruitment rate over the final 6 months of trial recruitment.

3.2.2.4 Trial Advertisement

In order to offer the trial to a wider population of potential patients who might not otherwise be able to access the trial if they were not already under the care of a severe asthma clinic at one of our recruiting centres we ran a number of media advertising campaigns to raise awareness and increase the profile of the trial.

TRIAL WEBSITE

At the start of the trial, a dedicated LASER trial website was developed (www.lasertrial.co.uk, see **Figure 3.6).** The website was approved by the ethics committee and was primarily designed to function as a resource for both trial participants and trial centre teams, providing information about TLA treatment and about the trial itself.

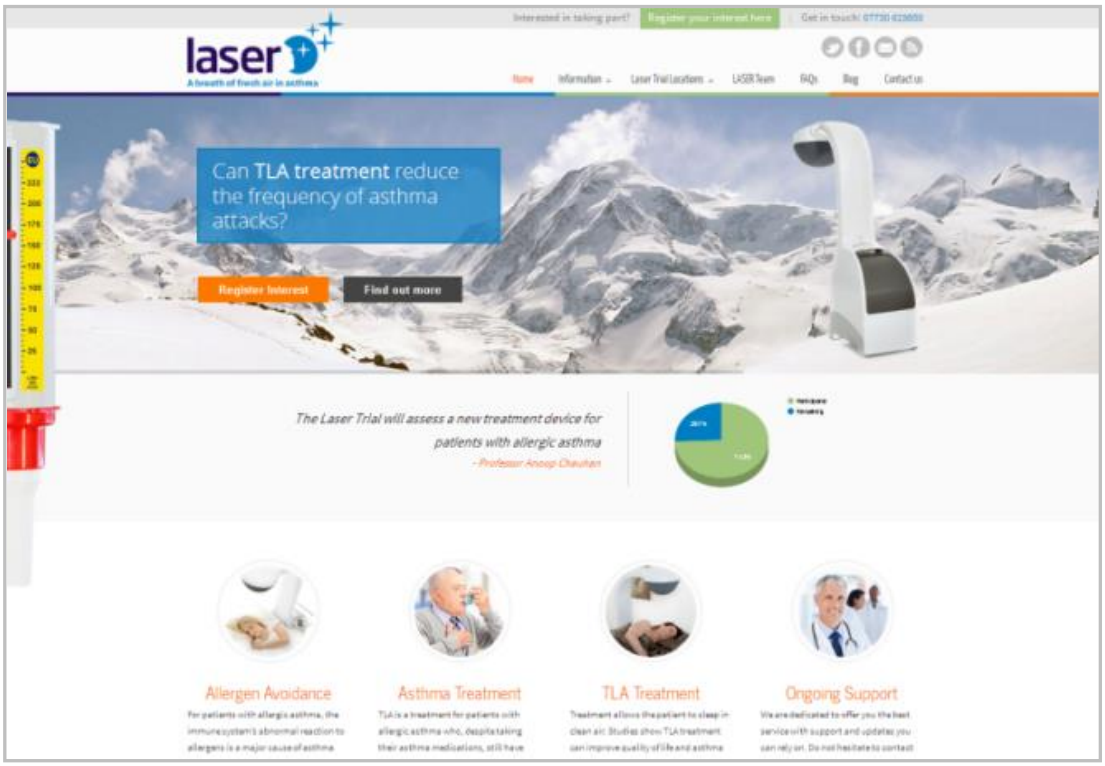


Figure 3.6 LASER trial website landing page

Within the website there were details about how to register interest in the trial. Visitors to the website could visit the 'Am I Eligible to Take Part' page on the website where they could submit details about their asthma to the trial team for consideration of their eligibility. The 7 'pre-screening' questions closely matched the trial eligibility criteria:

1. Age
2. Postcode
3. Smoking Status
4. Allergy Status
5. Number of exacerbations in the preceding 12 months
6. Current asthma treatment
7. Current asthma symptoms

An e-mail with the answers to these 7 questions was sent to a secure nhs.net e-mail account which was reviewed on a daily basis. Respondents who appeared to meet the trial eligibility criteria were

sent a trial PIS and put in contact with their nearest trial recruiting centre for formal assessment of eligibility.

This process was approved by the information governance framework of the Sponsor and that of its Caldicott Guardian.

The LASER trial website was used as the primary focus for the media advertising campaigns as a means of participants finding out more about the trial and registering their interest. During the course of the trial a total of 252 patients contacted the trial team through the website with responses to the 7 pre-screening questions. 86 patients were automatically excluded as they did not meet the trial entry criteria but of the remaining patients, after further contact and questioning, 66 were sent further details about the trial (PIS) and were put in contact with their closest recruiting centre.

All media campaigns also provided alternative contact details including a dedicated mobile telephone number and a text contact number ('Text LASER to 60777') to allow for individual preference in contacting the trial team.

TV COVERAGE

In September 2014, Professor Anoop Chauhan (the LASER Trial Chief Investigator) appeared alongside one of our trial participants in a news feature on BBC South Today. Following the broadcast, BBC South published the video on their Facebook and Twitter accounts. The Facebook post included a comment displaying the trial Web URL so that potential participants could access more information about the trial and, if interested, register for the trial. Using the Google Analytics tool, it was revealed that this social media interaction led to a significant increase in website traffic on the day of the broadcast, with 160 individual website sessions, as shown in **Figure 3.7**.

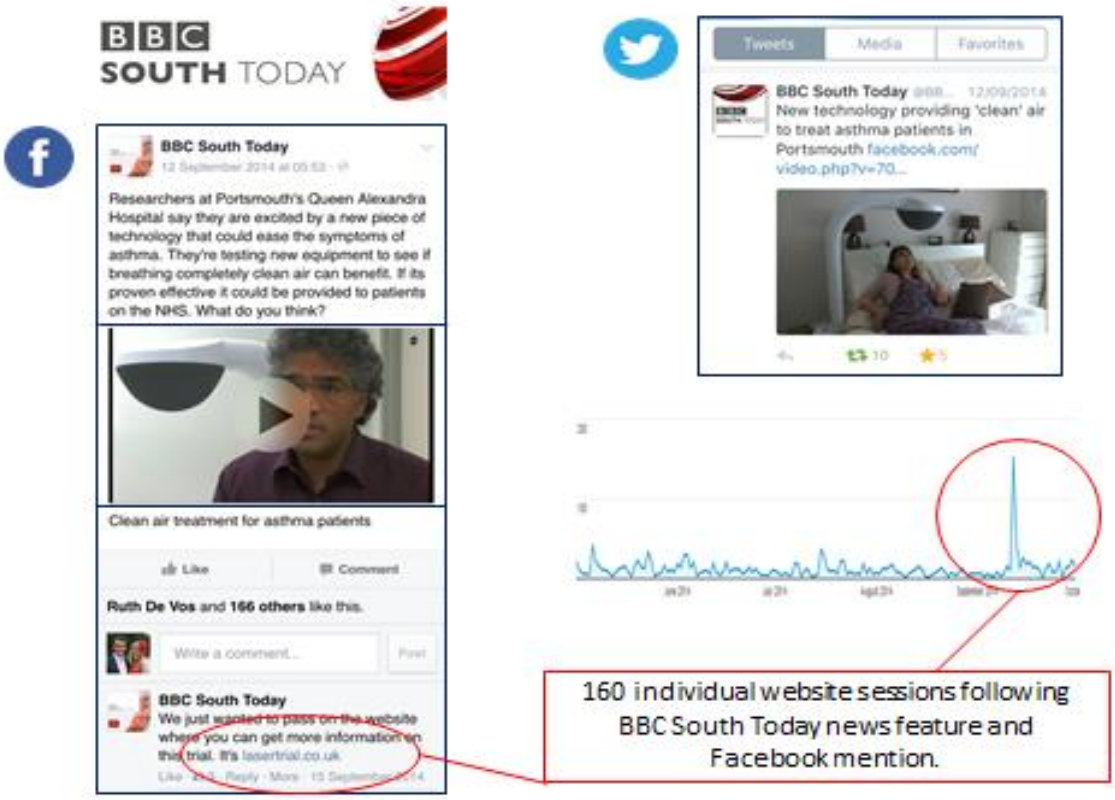


Figure 3.7 BBC South Social Media content and result

Social Media Advertising

Following on from this successful social media interaction, we recognised that social media advertising might be a useful strategy to improve access to the trial and increase recruitment.

The total population of the UK is 66.38 million and there are 44 million active social media users with the average user spending 1hr54mins/day on social media (We Are Social / Hootsuite 2018). These statistics continue to show a year on year increase in social media use.

Facebook remains the number 1 social media platform globally with a reach of 2.026 billion active users. The UK is ranked 10th in the world for Facebook use with a reach of 41 million users. In this context 'reach' refers to the figures Facebook releases for the total number of people that advertising on the Facebook platform may reach.

One advantage of Facebook and other social media advertising is that specific groups can be targeted by setting demographic and geographic parameters making it an ideal resource for targeted clinical trial recruitment campaigns.

Based on global values, a typical Facebook user 'Likes' 10 pages/30days, 'Comments' on 4 posts/30days and 'Clicks' on 8 Facebook adverts/30 days.

More evidence is emerging from both commercially driven and academic trials that social media is a useful tool in recruitment (Pederson et al 2015) (Frandsen et al 2016).

We developed a social media strategy for the LASER trial.

All social media postings were approved by the ethics committee and moderated by the trial team (Trial Co-ordinator and the Trial lead Research Nurse) who were involved in recruiting for the trial.

Social Media was employed in a number of different ways to raise awareness of the trial:

1. Partnering with Asthma / Allergy Charities

Firstly, we partnered with national charities with an interest in the new treatment, Asthma UK and Allergy UK, who publicised the trial on their websites and posted trial information both on Twitter and Facebook that signposted patients to the LASER Trial website – see **Figure 3.8** for example content from Asthma UK, which has 29,000 followers on Twitter and have had over 40,000 likes on Facebook. Allergy UK has 5,000 followers and have had >7,000 likes on Facebook.

Using Google Analytics, we saw a spike in activity on the website when posts/tweets were published, as shown in **Figure 3.9**.

Figure 3.8 Asthma UK website, Facebook and Twitter content

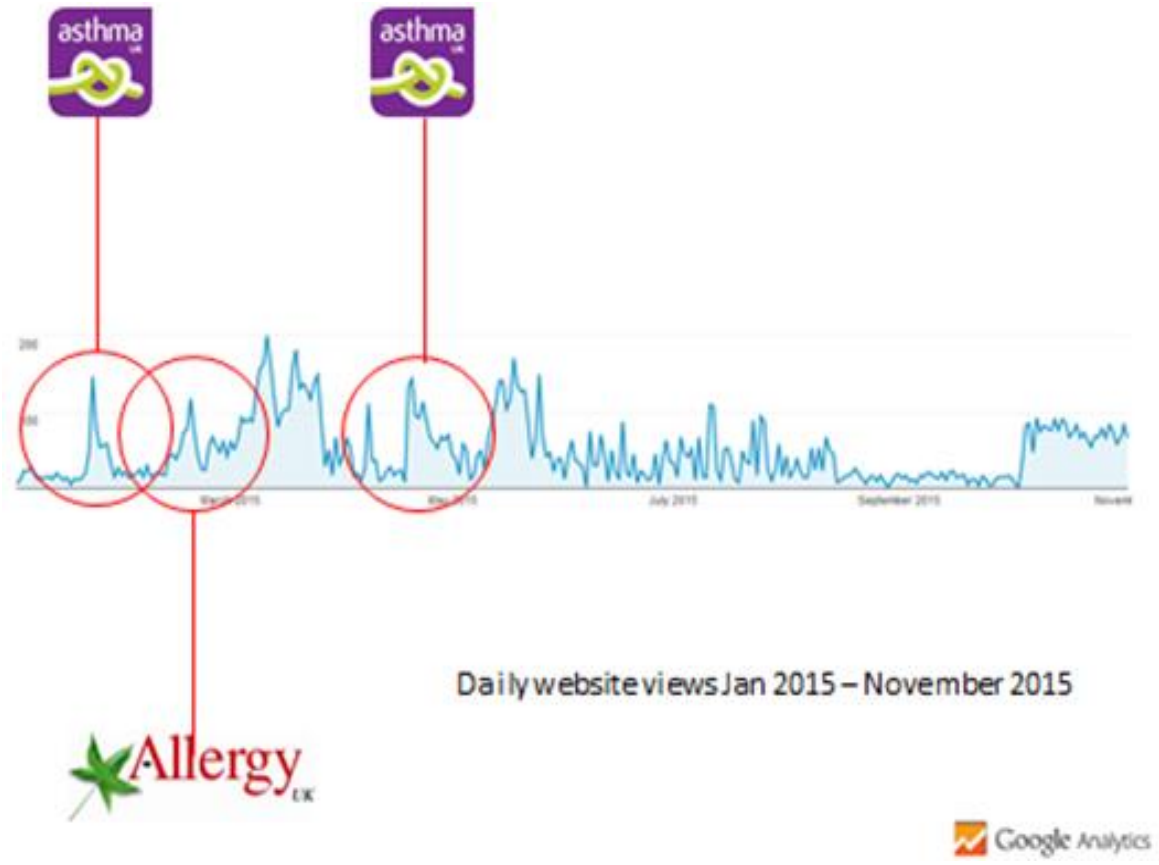


Figure 3.9 LASER website traffic with disease charity inputs

2. Facebook and Twitter Advertising

Secondly, we partnered with Tillison Consulting (https://tillison.co.uk) to develop a LASER trial Facebook page, and set up business accounts which facilitated trial advertisements on Facebook and Twitter such as that shown in **Figure 3.10**. This business account permits targeted advertising, enabling us to set demographic parameters based on trial inclusion criteria (age between 18 to 65 years, both men and women, location as 50km from a recruiting centre), and also to target people who have a search or following history which indicates an interest in asthma or asthma awareness. The tweets and posts directed people towards the LASER website and through to the screening questions. Techniques such as 'Google remarketing' were also used, in which people who had visited the website would be shown 'branded adverts' in the following 30-day period, although these were less successful than the social media campaigns.

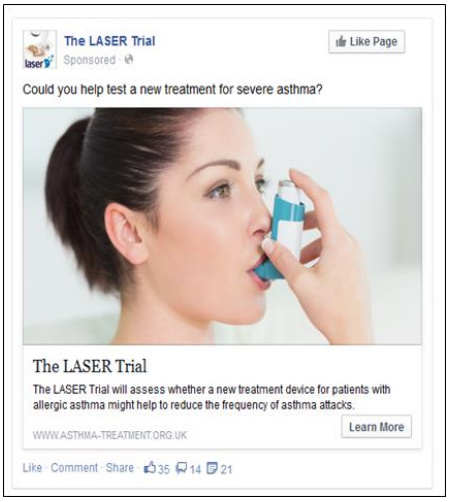


Figure 3.10 LASER trial Facebook advertisement

On Facebook we reached >100,000 individuals, had 1,361 clicks through to the LASER website, and were able to see a large number of patients engaging with the trial via 'likes', 'shares' and 'comments', which would have further increased the trial's visibility by sharing the information with friends or family with the condition. Similarly, on Twitter we reached over >150,000 people.

3. Trialbee

Finally, in March 2015 we partnered with the Swedish company Trialbee, which specialise in social media solutions for clinical trials. Trialbee advertised the trial on social media platforms, Facebook and Twitter. An advert (**Figure 3.11**) was displayed in the social media 'news-feed' of anyone who had previously expressed interest in asthma or had a search history including key words related to asthma. Demographic parameters enabled this to be restricted to the target age group and those within a commutable distance from one of the trial recruiting centres

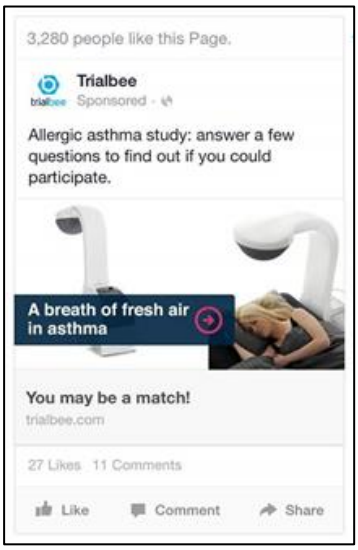


Figure 3.11 Trialbee Social Media Advert

If interested in the advert, clicking on a link diverted to the Trialbee websites dedicated LASER trial landing page (**Figure 3.12**) where there was detailed information about the trial.

Figure 3.12 Trialbee LASER trial landing page

On the Trialbee LASER trial page interested patients were able to answer a series of basic screening questions concerning their eligibility (**Figure 3.13**). and the details of those patients that passed this screening process were passed on to the LASER trial team at the respondents nearest recruiting centre to arrange further contact for formal eligibility screening.

Figure 3.13 Trialbee pre-screening questions

The 5 Trialbee pre-screening questions were answered 14,059 times, with 910 respondents meeting the basic eligibility requirements. Of these, and following more in-depth screening by the trial team, 57 were deemed eligible for the trial and 27 of these were subsequently consented and randomised to participate in the trial.

Newspaper Advertising

The LASER trial team worked with a media company with a track record in advertising for clinical trials, Media With Impact. A newspaper advert was designed to include the trial web URL and contact details for the trial team (**Figure 3.14**).

Newspaper adverts appeared in the local newspaper of our 5 leading trial centres over a 2-week period in March 2015.

This newspaper advert was approved by the ethics committee.

Figure 3.14 LASER Trial Newspaper Advertisement

RADIO ADVERTISING

Media With Impact also set up a 30 second radio advertisement which was broadcast on the local radio stations of the same 5 trial centres over the same 2 week period in March 2015. The radio advert's audio text included the following:

"Have you been told that you have allergic asthma? Have you had two or more asthma attacks in the last year? Well, it's time you heard about the LASER trial….

…On the LASER trial you will help us assess a new, non-drug treatment for asthma, in the hope that we can reduce asthma attacks in the future.

If you're aged 18-75, check if you're eligible on lasertrial.co.uk or text LASER to 60777.

LASER Trial, a breath of fresh air in asthma.

The LASER Trial is funded by the NIHR"

The radio advert audio text was approved by the ethics committee.

3.3 RECRUITMENT TO TIME AND TARGET

These combined strategies resulted in an increased rate of recruitment (**Figure 3.15**). The revised recruitment trajectory was met (**Figure 3.16**) and the recruitment target ultimately exceeded (240 participants recruited instead of 222) because the 2-week screening period meant that a number of new participants had already entered the screening period once the recruitment target had been met. It was felt unethical to exclude these participants on the basis of meeting a target.

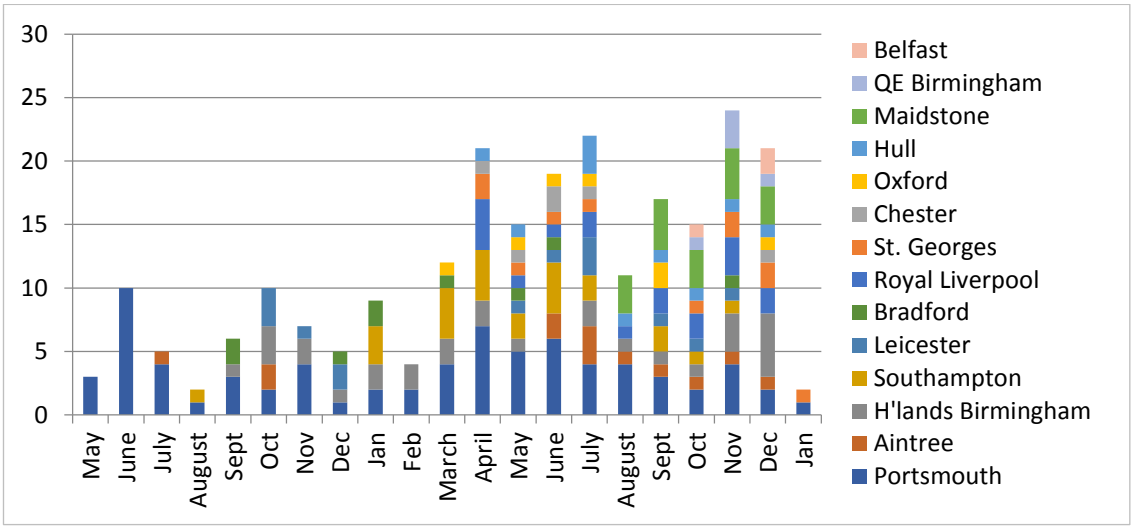


Figure 3.15 Monthly Recruitment Rate

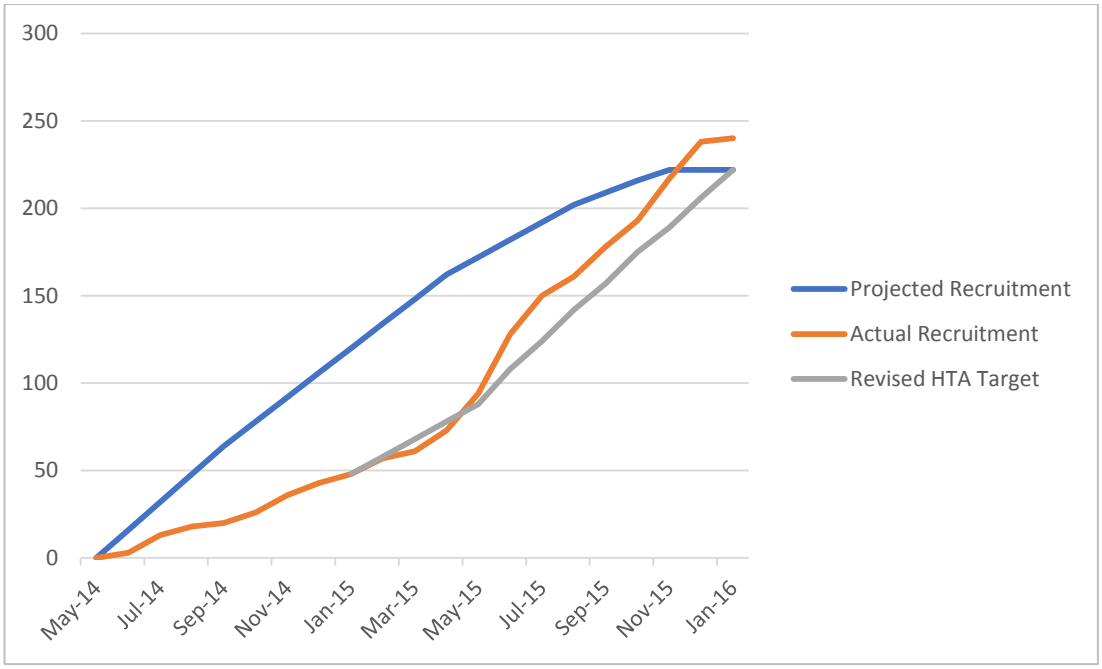


Figure 3.16 Participant recruitment rates

3.4 Recruitment Sources

Table 3.2 lists the sources that referred the 240 recruited participants to the trial. 80% of participants were recruited from existing cohorts of patients at the 14 recruiting centres. The majority of the remaining participants were recruited through social media channels, which are described in detail in **Section 3.2.2.4** *Social Media Advertising***.** The Trialbee social media campaign was notably successful with 16% of participants recruited during the period that the campaign was active (Mar-Dec 2015) being recruited through this channel.

Table 3.2 Participant referral sources

Referral Source	**Randomised Participants (%)**
Existing Clinic Patient	192 (80%)
Social Media (Trialbee)	27 (11%)
Social Media (Asthma UK / Allergy UK / Tillison)	13 (5%)
Newspaper Advertisement	0
Radio Advertisement	1 (<1%)

Other	7 (3%)
Total	**240**

CHAPTER 4 QUANTITATIVE RESULTS

4.1 PARTICIPANTS

4.1.1 RECRUITMENT

Screening and recruitment for the LASER trial took place between 25th May 2014 and 11th January 2016, resulting in the randomisation of 240 participants. A total of fourteen centres randomised participants into the trial. The randomisation of participants by recruiting centre are listed in **Table 4.1**.

Table 4.1 Randomisations by Centre

Recruiting Centres	Placebo, n (% of treatment group)	Active, n (% of treatment group)	Total, n (% of all participants)
ALL	**121**	**119**	**240**
Belfast	1 (1%)	2 (2%)	3 (1%)
Birmingham-Heartlands	15 (12%)	13 (11%)	28 (12%)
Birmingham-Queen Elizabeth	3 (2%)	2 (2%)	5 (2%)
Bradford	4 (3%)	5 (4%)	9 (4%)
Chester	3 (2%)	3 (3%)	6 (3%)
Hull	6 (5%)	4 (3%)	10 (4%)
Leicester	7 (6%)	7 (6%)	14 (6%)
Liverpool-Aintree	5 (4%)	8 (7%)	13 (5%)
Liverpool-Royal	8 (7%)	10 (8%)	18 (8%)
London	6 (5%)	5 (4%)	11 (5%)
Maidstone	9 (7%)	8 (7%)	17 (7%)
Oxford	3 (2%)	4 (3%)	7 (3%)
Portsmouth	38 (31%)	36 (30%)	74 (31%)
Southampton	13 (11%)	12 (10%)	25 (10%)

4.1.2 Baseline Characteristics

The baseline characteristics of the 240 participants randomised into the two participant groups are summarized in **Table 4.2**. The 5 participants who withdrew consent to use previously collected data (see Section 4.1.4 for details) are indicated by "~Missing".

These baseline data indicate that the two participant groups are proportionately balanced.

Table 4.2 Participant baseline characteristics

Factor	Level	Placebo, n (% of treatment group, N = 121)	Active, n (% of treatment group, N = 119)	Total, n (% of all participants N = 240)
Origin of case				
New to clinic (incident) or existing patient (prevalent)	Incident	26 (21%)	24 (20%)	50 (21%)
	Prevalent	94 (78%)	91 (76%)	185 (77%)
	~Missing	1 (1%)	4 (3%)	5 (2%)
Demographics				
Gender	Female	90 (74%)	82 (69%)	172 (72%)
	Male	30 (25%)	33 (28%)	63 (26%)
	~Missing	1 (1%)	4 (3%)	5 (2%)
Age at Randomisation (yrs)	16-17	1 (1%)	0 (0%)	1 (<1%)
	18-34	33 (27%)	26 (22%)	59 (25%)
	35-59	69 (57%)	70 (59%)	139 (58%)
	60-75	17 (14%)	19 (16%)	36 (15%)
	~Missing	1 (1%)	4 (3%)	5 (2%)
Age at Randomisation (yrs), mean (SD)		45.3 (13.8), n=120	46.8 (13.8), n=115	46.1 (13.8), n=235
Ethnicity	White	103 (85%)	100 (84%)	203 (85%)
	Bangladeshi	1 (1%)	0 (0%)	1 (<1%)
	Black Caribbean	1 (1%)	2 (2%)	3 (1%)
	Black Other	1 (1%)	0 (0%)	1 (<1%)
	Indian	5 (4%)	4 (3%)	9 (4%)
	Mixed White	2 (2%)	2 (2%)	4 (2%)
	Other	1 (1%)	2 (2%)	3 (1%)
	Pakistani	5 (4%)	4 (3%)	9 (4%)
	UNK	1 (1%)	1 (1%)	2 (1%)
	~Missing	1 (1%)	4 (3%)	5 (2%)
Category of Body Mass Index (kg/m^2)	Severely underweight (15-16)	1 (1%)	1 (1%)	2 (1%)
	Normal (18.5-25)	24 (20%)	26 (22%)	50 (21%)
	Overweight (25-30)	33 (27%)	38 (32%)	71 (30%)
	Obese Class I (30-35)	33 (27%)	26 (22%)	59 (25%)
	Obese Class II (35-40)	9 (7%)	17 (14%)	26 (11%)
	Obese Class III (40 or over)	18 (15%)	6 (5%)	24 (10%)
	~Invalid data	2 (2%)	1 (1%)	3 (1%)
	~Missing	1 (1%)	4 (3%)	5 (2%)
Body Mass Index (kg/m2), mean (SD)		31.2 (7.2) n=120	29.6 (5.9) n=115	30.4 (6.6) n=135

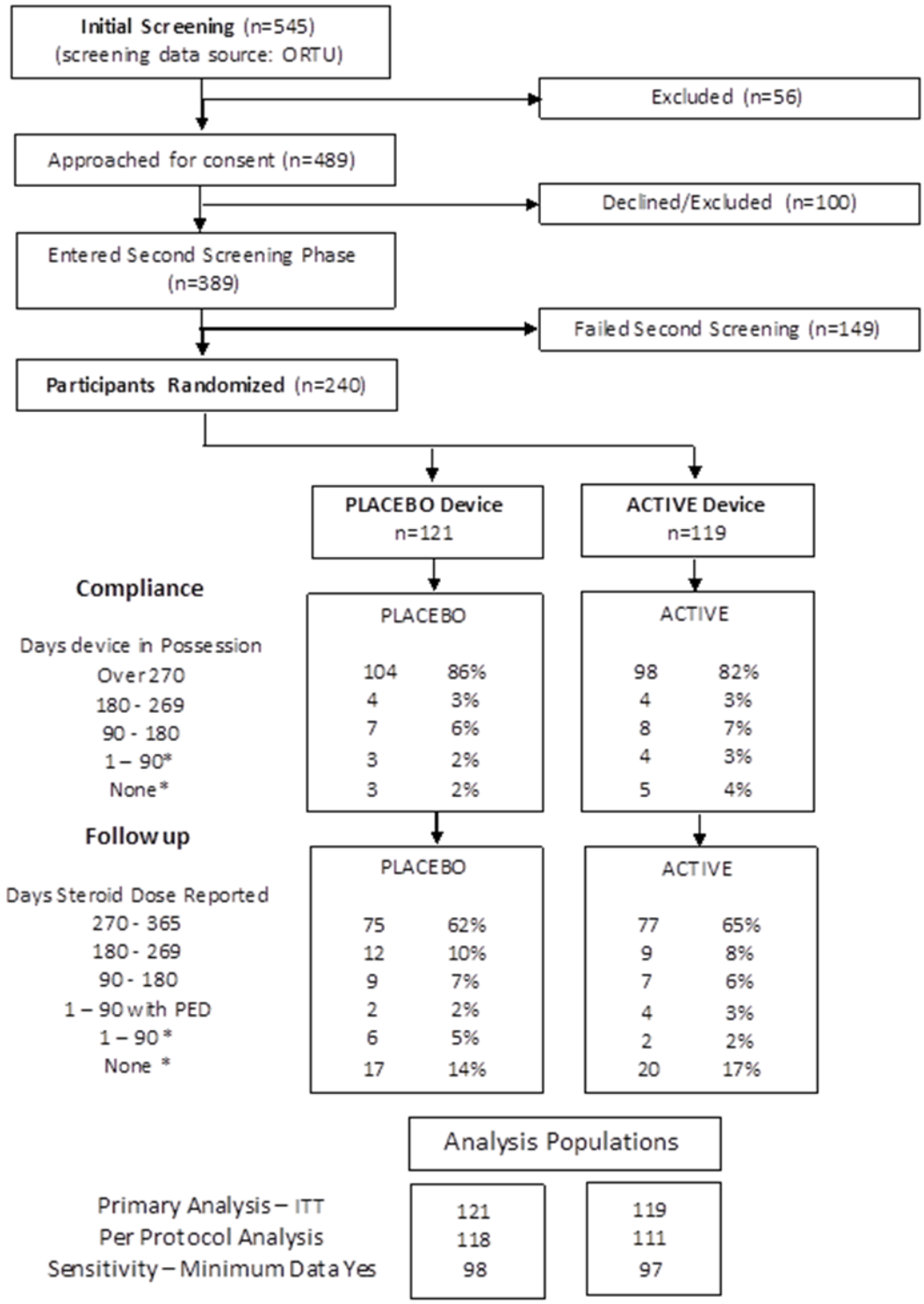
Smoking				
Smoking status	Ex-smoker	36 (30%)	22 (18%)	58 (24%)
	Never smoked	84 (69%)	93 (78%)	177 (74%)
	~Missing	1 (1%)	4 (3%)	5 (2%)
Does anyone smoke in the bedroom where the TLA will be installed?	No	120 (99%)	115 (97%)	235 (98%)
	~Missing	1 (1%)	4 (3%)	5 (2%)
Does anyone smoke in the house?	No	116 (96%)	112 (94%)	228 (95%)
	Yes	4 (3%)	3 (3%)	7 (3%)
	~Missing	1 (1%)	4 (3%)	5 (2%)
Exacerbation history				
Exacerbation frequency in preceding 12 months*	2	38 (31%)	37 (31%)	75 (31%)
	3	30 (25%)	27 (23%)	57 (24%)
	>3	52 (43%)	51 (43%)	103 (43%)
	~Missing	1 (1%)	4 (3%)	5 (2%)
Number of exacerbations in preceding 12 months, mean (SD)		4.3 (3.7), n=116	3.5 (1.8), n=112	3.9 (2.9), n=228
Hospital admissions in preceding 12 months	00	81 (66.9%)	80 (67.2%)	161 (67.1%)
	01	21 (17.4%)	17 (14.3%)	38 (15.8%)
	02	8 (6.6%)	11 (9.2%)	19 (7.9%)
	03	6 (5.0%)	2 (1.7%)	8 (3.3%)
	04	1 (0.8%)	4 (3.4%)	5 (2.1%)
	06	1 (0.8%)	0 (0.0%)	1 (0.4%)
	07	0 (0.0%)	1 (0.8%)	1 (0.4%)
	10	1 (0.8%)	0 (0.0%)	1 (0.4%)
	12	1 (0.8%)	0 (0.0%)	1 (0.4%)
	~Missing	1 (0.8%)	4 (3.4%)	5 (2.1%)
Previous asthma related ITU admission	No	96 (79%)	87 (73%)	183 (76%)
	Yes	24 (20%)	28 (24%)	52 (22%)
	~Missing	1 (1%)	4 (3%)	5 (2%)
Physiological measures				
Pre-bronchodilator FEV_1 > 50%	No	28 (23%)	27 (23%)	55 (23%)
	Yes	92 (76%)	88 (74%)	180 (75%)
	~Missing	1 (1%)	4 (3%)	5 (2%)
Pre-Bronchodilator FEV_1 (litres)		2.0 (0.8), n=118	2.1 (0.9), n=115	2.1 (0.8), n=233
Pre-Bronchodilator FEV_1 Percent		68.5 (21.7), n=118	69.9 (22.6), n=115	69.2 (22.1), n=233
Pre-Bronchodilator FVC		3.0 (1.0), n=118	6.2 (33.9), n=115	4.6 (23.9), n=233
Pre-Bronchodilator FVC Percent		86.4 (19.4), n=118	88.3 (17.5), n=115	87.4 (18.5), n=233
F_ENO (ppb)		36.3 (36.0), n=114	38.7 (35.7), n=110	37.5 (35.8), n=224
Asthma treatments				
Use of maintenance corticosteroids?	No	91 (75%)	86 (72%)	177 (74%)
	Yes	29 (24%)	29 (24%)	58 (24%)

	~Missing	1 (1%)	4 (3%)	5 (2%)
Category of Baseline dose of Maintenance Steroid (mgs/day, prednisolone equivalent)	1- 9	10 (8%)	13 (11%)	23 (10%)
	10-19	5 (4%)	12 (10%)	17 (7%)
	20-29	5 (4%)	0 (0%)	5 (2%)
	30	1 (1%)	1 (1%)	2 (1%)
	40	2 (2%)	1 (1%)	3 (1%)
	None	97 (80%)	88 (74%)	185 (77%)
	~Missing	1 (1%)	4 (3%)	5 (2%)
Steroid sparing immunosuppressant?	No	115 (95%)	109 (92%)	224 (93%)
	Yes	5 (4%)	6 (5%)	11 (5%)
	~Missing	1 (1%)	4 (3%)	5 (2%)
Monoclonal antibody therapy?	No	105 (87%)	106 (89%)	211 (88%)
	Yes	15 (12%)	9 (8%)	24 (10%)
	~Missing	1 (1%)	4 (3%)	5 (2%)
Bronchial Thermoplasty?	No	119 (98%)	112 (94%)	231 (96%)
	Yes	1 (1%)	3 (3%)	4 (2%)
	~Missing	1 (1%)	4 (3%)	5 (2%)

* All participants should have experienced at least two exacerbations in the previous 12 months to enter the study

4.1.3 Participant Flow

The overall flow of the 240 participants randomised into the trial is shown in **Figure 4.1**. This diagram shows the compliance of the two participant groups to device usage (measured as days in possession of device during the 365 days of their trial participation), as well as their compliance to reporting of steroid dose (again number of days steroid dose reported during the 365 days of their trial participation). There was a requirement for participants to remain active in the trial for a minimum of 6 months before they became eligible for four years' post-trial provision of the active device.



*Did not meet minimum data criteria of at least one reported PED and/or 90 days of reporting dosage taken. In the main analysis, all participants were included using the available data from all dated sources verified by dosage information when available. For sensitivity analyses, estimates of the number of exacerbation were substituted for those that did not meet minimum data criteria.

Figure 4.1 LASER CONSORT: Participants Randomised (n=240)

4.1.4 WITHDRAWALS

59 participants either did not have minimum data, died, or had a withdrawal form completed (Appendix M – Table M1). In some cases, data was provided after the withdrawal date, bringing into question the withdrawal status. In other cases, the withdrawals were participants lost to follow-up. Five participants withdrew consent for the use of previously collected data. All participants were included in the primary analysis and the CONSORT table provides data on when the devices were removed. Of the 59 participants, 31 were in the active group and 28 were in the placebo group.

4.1.5 MISSING DATA

Steroid dose is the key indicator of the primary outcome and unfortunately a considerable amount of this data was not collected from the primary outcome data sources (as shown in Section 4.2.1).

For both active and placebo groups, we calculated the total possible study days from the date of randomisation to 12 month Follow-up Visit if available, or 365 days post-randomisation if no 12 month Follow-up Visit occurred. If participants withdrew earlier than 12 months, the study days were calculated from randomisation to the point of withdrawal.

Placebo group

29,147 (66.1%) of the 44,091 possible study days of daily maintenance steroid use was collected on the Placebo group. 6419 (22.0%) of the 29,147 days of maintenance dose information analysed are based on the assumption of zero dose because these data were left blank but other fields of the daily diary (i.e. any of device use, reliever use or time off work) were completed.

In addition to missing maintenance steroid dose data, there were missing exacerbation steroid dose data. 30 mg dose was assumed for the 24 days of Placebo group cases where exacerbation dose data was left blank in the PED.

Active group

28,753 (65.3%) of the 43,398 possible study days of maintenance steroid dose information was collected on the Active group. 4819 (16.8%) of the 28,753 days of maintenance dose information analysed are based on the assumption of zero dose because these dose data were left blank but other fields of the daily diary were completed.

In addition to missing maintenance steroid dose data, there were missing exacerbation steroid dose data. 30 mg dose was assumed for the 25 days of Active group cases where exacerbation dose data was left blank in the PED.

Table 4.3 Missing data summary

	Placebo	Active
Possible study days: days from Randomisation to 12 month Follow-up Visit (or 365 days, if later), mean (SD)	373.5 (16.2)	376.0 (22.2)
Days where dose was reported by participant on daily diary or severe exacerbation report, mean (SD)	244.2 (133.7)	245.7 (137.3)
Days where zero dose was assumed, mean (SD)	54.1 (89.8)	41.5 (77.6)

4.2. OUTCOMES

4.2.1 PRIMARY OUTCOME SOURCES OF DATA

Data pertaining to the primary outcome were reported in several sources, as described in Section 2.11.2.2. Only 18% of the dated severe exacerbations were reported in all three expected sources: 1. TLA Diary (TLA), 2. Exacerbation Diary (PED) and 3. Exacerbation Review Form (REV). 40 (12%) of the severe exacerbations were only reported on the REV, with no other supporting data.

The number of participants reporting none, one or more dated exacerbations between treatment groups during the 12 months of the trial is shown in **Table 4.4**.

Table 4.4 Number of participants reporting none, one or more dated exacerbations between treatment groups during the 12 months of the trial

Number	Placebo	Active	Total
	N=121	N=119	N=240
0	55 (45%)	49 (41%)	104 (43%)
1	23 (19%)	25 (21%)	48 (20%)
2	17 (14%)	16 (13%)	33 (14%)
3	9 (7%)	16 (13%)	25 (10%)
4	7 (6%)	8 (7%)	15 (6%)
5	3 (2%)	3 (3%)	6 (3%)
6	2 (2%)	1 (1%)	3 (1%)
7	2 (2%)	1 (1%)	3 (1%)
8	2 (2%)	0 (0%)	2 (1%)
10	1 (1%)	0 (0%)	1 (<1%)

4.2.2 Primary Outcome

As shown in **Table 4.5**, there was no statistical difference in the rate of severe exacerbations between the two participant groups (p = 0.62).

Table 4.5 Primary Outcome: Frequency of severe asthma exacerbations occurring within the 12-month follow-up period

	Placebo			Active			Risk Ratio *	SD	95% CI	P value
	N / events	Mean	SD	N / events	Mean	SD				
Total Dated Severe exacerbations within 1 year	121 / 179	1.48	2.03	119 / 165	1.39	1.57	0.92	0.15	0.66 to 1.27	0.6167
Dated Severe exacerbations within 1 year Per-protocol Population	118 / 179	1.52	2.04	111 /164	1.48	1.59	0.951	0.15	0.69 to 1.31	0.7575

* Adjusted for the minimisation factors

4.2.2.1 Sensitivity Analysis

The sensitivity analyses designed to test the robustness of the results to the missing data as described in Section 2.11.2.4 show that the primary outcome results in Table 4.7 are very sensitive to these assumptions; by varying these assumptions the primary outcome treatment effects could go either way. This conclusion was drawn by investigating the best and worst case scenarios for those participants who did not meet the minimum data requirement (see Section 2.11.2.4 for definition). The following best and worst case scenarios describe the best and worst numbers of severe exacerbations that might have occurred in this population of 45 participants during the 12 month trial period, but that were not captured in the primary outcome dataset:

Modified best and worst case:

- Best case = 0
- Worst case = 4

The results of the sensitivity analyses made using the best and worst case scenarios are:

The point estimates of the risk ratio ranged from 1.4 (worst for active) to 0.6 (best for active) in the modified best and worst case analysis highlighting the wide range of possible outcomes under different assumptions about the outcomes for those with less than the minimum amount of data reported.

The amount of missing data could mask a difference between the treatments, but this could be in either direction.

4.2.2.2. POST-HOC ANALYSIS OF PRIMARY OUTCOME DATA

Following review of recently reported literature where exacerbations have been defined with a less stringent definition, the original definition of primary endpoint (see Section 2.4.1) was amended so that comparison with these studies could be undertaken. In the new definition, an exacerbation was defined as a 10 mg increase in steroid dose over any maintenance dose for 3 consecutive days. All other parts of the definition remained the same, i.e. separate exacerbations were identified by at least 7 days at or below maintenance dose.

The primary outcome calculated for this new primary endpoint definition is presented in **Table 4.6**. This analysis also supports no rejection of the hypothesis of no difference between the treatment groups and therefore provides the same conclusion of the primary outcome as the analysis performed according to the original definition of primary endpoint.

Table 4.6 Primary outcome results - alternative definition of primary endpoint post-hoc analysis

Post-hoc analysis	Placebo			Active			Risk Ratio*	SD	95% CI	P value
	N / events	Mean	SD	N / events	Mean	SD				
New definition of exacerbation steroid dose	121 / 186	1.54	2.05	119 / 189	1.59	1.75	1.02	0.17	0.7 to 1.4	0.910

4.2.3 Quantitative Secondary Outcomes

4.2.3.1 Asthma Control

The Asthma Control secondary outcome results (Lung function, Asthma Control Questionnaire (ACQ) score, Asthma Control Diary (ACD) score and Sino-Nasal Outcome Test (SNOT-22) score) are presented in **Table 4.7**.

The only Asthma Control secondary outcome that was found to be statistically significant was daily maximum Peak Flow ($p = 0.045$). All other aspects of the Lung Function secondary outcome (Pre-bronchodilator FEV_1, Fractional exhaled Nitric Oxide (F_ENO) and Post-bronchodilator FEV_1) as well as ACQ, ACD and SNOT-22 scores were not found to be statistically significant. It should be noted that due to the fact that there was a large amount of missing peak flow data, and that the one significant result emerges against six non-significant results (the multiple testing problem), this significant result could have occurred by chance.

Table 4.7 Secondary outcomes: Lung function, ACQ Scores and SNOT-22 Scores.

Outcome	Timepoint	Placebo			Active						
		N	Mean	SD	N	Mean	SD	Treatment effect	SD	95% CI	P value
Lung function											
Pre-bronchodilator FEV_1	Screening	119	2.02	0.86	113	2.01	0.84				
	Randomisation	118	2.02	0.81	115	2.09	0.86				
	3 months	100	2 .05	0.76	98	2.14	0.89				
	6 months	100	2.04	0.81	94	2.16	0.86				
	9 months	92	1.99	0.79	88	1.98	0.78				
	12 months	91	2.01	0.79	85	2.01	0.8				
Pre-bronchodilator FEV_1 Mixed Model Analysis								-0.014	0.05	-0.11 to 0.08	0.7607
Fractional exhaled Nitric Oxide (F_ENO)	Screening	0	n/a	n/a	0	n/a	n/a				
	Randomisation	114	36.35	35.98	110	38.74	35.74				
	3 months	97	35.13	34.81	95	34.06	32.03				
	6 months	95	32.67	35.07	91	32.71	30.67				
	9 months	87	30.31	29.2	81	36.45	37.33				
	12 months	89	33.39	33.11	82	32.56	30.19				
Fractional exhaled Nitric Oxide (F_ENO) Mixed Model Analysis								-1.843	2.58	-6.91 to 3.22	0.4756

Outcome	Timepoint	Placebo			Active						
		N	Mean	SD	N	Mean	SD	Treatment effect	SD	95% CI	P value
Lung Function contd.											
Post-bronchodilator FEV_1	Screening	115	2.32	0.85	111	2.27	0.84				
	Randomisation	0	n/a	n/a	0	n/a	n/a				
	3 months	0	n/a	n/a	0	n/a	n/a				
	6 months	0	n/a	n/a	0	n/a	n/a				
	9 months	0	n/a	n/a	0	n/a	n/a				
	12 months	81	2.17	0.77	84	2.24	0.8				
Post-bronchodilator FEV_1 Regression Analysis								0.04	0.05	-0.07 to 0.15	0.4628
Average daily maximum Peak Flow	Screening	91	311.22	117.84	82	336.62	126.78				
	Randomisation	0	0	n/a	n/a	0	n/a				
	3 months	93	321.52	118.68	87	341.24	130.94				
	6 months	87	319.66	124.62	91	351.11	130.95				
	9 months	80	307.97	112.97	80	338.3	130.52				
	12 months	76	319.72	121.46	74	349.83	124.5				
Average daily maximum Peak Flow Mixed Model Analysis								14.729	7.35	0.32 to 29.14	0.0452
Patient Reported Outcomes											
ACQ Score	Screening	107	2.98	0.99	107	2.9	0.96				
	Randomisation	110	3.05	1.08	106	2.84	1				
	3 months	81	2.54	1.27	84	2.26	1.02				
	6 months	89	2.55	1.27	84	2.24	1.03				

	9 months	83	2.45	1.21	78	2.38	1.18				
	12 months	82	2.42	1.28	79	2.31	1.16				
ACQ Score Mixed Model Analysis								-0.054	0.11	-0.26 to 0.15	0.6061
Outcome	**Timepoint**	**Placebo**			**Active**						
		N	**Mean**	**SD**	**N**	**Mean**	**SD**	**Treatment effect**	**SD**	**95% CI**	**P value**
Patient Reported Outcomes contd.											
ACD scores averaged over available 14 Days	Screening	32	2.08	1	31	2.18	1.19				
	Randomisation	0	n/a	n/a	0	n/a	n/a				
	3 months	36	1.42	1.02	28	1.84	1.37				
	6 months	33	1.68	1.35	37	1.96	1.19				
	9 months	26	1.8	1.17	34	2.02	1.22				
	12 months	36	1.59	1.08	34	1.94	1.27				
ACD scores averaged over available 14 Days Mixed Model Analysis								0.212	0.25	-0.28 to 0.71	0.4008
Sino Nasal Outcome Test (SNOT-22) score	Screening	0	n/a	n/a	0	n/a	n/a				
	Randomisation	120	41.17	21.74	114	41.78	21.32				
	3 months	106	38.53	21.28	100	34.95	20.95				
	6 months	101	39.33	22.25	97	34.16	20.7				
	9 months	95	37.99	22.38	89	35.24	22.12				
	12 months	96	36.3	23.57	90	35.69	21.18				
Sino Nasal Outcome Test (SNOT-22) score Mixed Model Analysis								-3.265	1.85	-6.9 to 0.37	0.0781

4.2.3.2 Quality of Life

Asthma Related Quality of Life

The two participant groups had similar overall AQLQ(S) scores at randomisation (p=0.213, **Table 4.8**). In both participant groups there was a statistically significant improvement in overall quality of life over the trial. When quality of life at 12 months was compared to that at randomisation, an improvement in the overall AQLQ(S) score of 0.57 (p<0.001) in the placebo group and 0.68 (p<0.001) in those receiving the TLA device was identified. Although, the improvement in overall quality of life was higher in participants in the TLA group, this improvement was not statistically significant when compared to participants in the placebo group (p=0.543).

Overall AQLQ(S) scores between the two participant groups were similar at each follow-up visit, except at 6 months, where participants receiving the TLA device had a significantly higher quality of life than those receiving placebo (4.74 vs. 4.30, respectively; p=0.020). This difference at 6 months was also observed for the following domains: activity limitation (p=0.022) and environmental stimuli (p=0.009). In addition, participants in the Active TLA group also had higher quality of life scores in the domain for environmental stimuli at 9 months (p=0.038).

Table 4.8 Responses to the AQLQ(S)

	Placebo, mean (S.D)	**Active**, mean (S.D)	**P Value**	**Mean difference** (95% CI)
Overall score, across all 4 domains				
Randomisation	3.87 (1.22) n=120	4.07 (1.20) n=115	0.213	0.20 (-0.11 to 0.51)
3 months	4.39 (1.41) n=107	4.67 (1.25) n=100	0.139	0.27 (-0.09 to 0.65)
6 months	4.30 (1.42) n=101	4.74 (1.22) n=97	0.020	0.44 (0.07 to 0.81)
9 months	4.36 (1.53) n=95	4.65 (1.35) n=90	0.166	0.29 (-0.12 to 0.72)
12 months	4.50 (1.47) n=96	4.76 (1.33) n=90	0.219	0.25 (-0.15 to 0.66)
Difference at 12m	0.57 (1.12) n=96	0.68 (1.24) n=90	0.543	0.11 (-0.24 to 0.45)

Symptoms Domain				
Randomisation	3.74 (1.28)	3.93 (1.21)	0.233	0.19 (-0.13 to 0.51)
3 months	4.35 (1.51)	4.59 (1.34)	0.239	0.23 (-0.15 to 0.63)
6 months	4.25 (1.53)	4.63 (1.28)	0.061	0.38 (-0.02 to 0.78)
9 months	4.36 (1.57)	4.58 (1.46)	0.319	0.22 (-0.22 to 0.66)
12 months	4.56 (1.54)	4.62 (1.36)	0.761	0.06 (-0.36 to 0.49)
Difference at 12m	0.74 (1.29)	0.69 (1.32)	0.816	-0.04 (-0.42 to 0.33)
Activity Limitation Domain				
Randomisation	4.02 (1.29)	4.29 (1.30)	0.103	0.28 (-0.06 to 0.61)
3 months	4.47 (1.41)	4.76 (1.34)	0.141	0.28 (-0.09 to 0.66)
6 months	4.39 (1.43)	4.84 (1.28)	0.022	0.45 (0.07 to 0.83)
9 months	4.41 (1.54)	4.75 (1.43)	0.121	0.34 (-0.09 to 0.77)
12 months	4.54 (1.49)	4.92 (1.35)	0.070	0.38 (-0.03 to 0.79)
Difference at 12m	0.47 (1.09)	0.62 (1.19)	0.394	0.14 (-0.19 to 0.47)
Emotional Function Domain				
Randomisation	3.83 (1.58)	3.95 (1.47)	0.572	0.11 (-0.28 to 0.51)
3 months	4.36 (1.73)	4.72 (1.52)	0.111	0.36 (-0.08 to 0.81)
6 months	4.21 (1.79)	4.67 (1.58)	0.055	0.46 (-0.01 to 0.94)
9 months	4.33 (1.92)	4.55 (1.59)	0.399	0.22 (-0.29 to 0.73)
12 months	4.39 (1.82)	4.68 (1.68)	0.257	0.29 (-0.22 to 0.80)
Difference at 12m	0.51 (1.36)	0.76 (1.59)	0.259	0.25 (-0.18 to 0.67)
Environmental Stimuli Domain				
Randomisation	3.92 (1.51)	4.02 (1.52)	0.599	0.10 (-0.29 to 0.49)
3 months	4.38 (1.56)	4.62 (1.57)	0.277	0.24 (-0.19 to 0.67)
6 months	4.32 (1.64)	4.90 (1.44)	0.009	0.58 (0.14 to 1.01)
9 months	4.25 (1.63)	4.73 (1.45)	0.038	0.48 (0.03 to 0.93)
12 months	4.36 (1.65)	4.79 (1.59)	0.070	0.43 (-0.04 to 0.90)
Difference at 12m	0.41 (1.42)	0.69 (1.53)	0.205	0.28 (-0.15 to 0.70)

GENERIC HEALTH RELATED QUALITY OF LIFE

Responses to the EQ-5D-5L questionnaire are presented in **Table L1**. The utilities that these responses were converted into are shown in **Table 4.9**. For participants who completed the EQ-5D at both randomisation and 12 months there was no statistically significant improvement in overall quality of life over the trial in either participant group (p=0.983 for the placebo group and p=0.105 for the TLA device group). No significant differences in utility values were observed between the two groups at any of the follow-up visits either (using data complete for each follow-up visit only).

Table 4.9 also shows that there was a statistically significant improvement in overall quality of life over the trial in both participant groups when assessed by EQ-VAS scores. When quality of life at 12 months was compared to that at randomisation, an improvement in VAS scores of 7 was observed both for the placebo and those receiving the TLA device (p=0.002 and p=0.001, respectively). At 3 months, participants in the TLA device group had significantly higher VAS scores than those in the placebo group (65 vs.59; p=0.032)

Table 4.9 EQ-5D-5L utility and visual analogue scale (VAS) scores

	Placebo	**Active**	**P Value**	**Mean difference** (95% CI)
EQ-5D-5L utility, mean (S.D).				
Randomisation	0.67 (0.25) n=119	0.68 (0.26) n=115	0.633	0.02 (-0.05 to 0.08)
3 months	0.68 (0.27) n=104	0.73 (0.23) n=98	0.123	0.05 (-0.01 to 0.12)
6 months	0.67 (0.28) n=101	0.71 (0.24) n=96	0.265	0.04 (-0.03 to 0.12)
9 months	0.64 (0.30) n=95	0.72 (0.22) n=90	0.052	0.08 (-0.00 to 0.15)
12 months	0.67 (0.30) n=96	0.74 (0.24) n=90	0.081	0.07 (-0.01 to 0.15)
Difference at 12m	-0.00 (0.17) n=96	0.03 (0.17) n=90	0.226	0.04 (-0.02 to 0.08)
EQ-VAS score, mean (S.D).				
Randomisation	58 (20) n=120	61 (19) n=115	0.329	2 (-2 to 7)
3 months	59 (23) n=104	65 (18) n=98	0.032	6 (1 to 12)

6 months	63 (21) n=102	64 (20) n=95	0.690	1 (-5 to 7)
9 months	62 (21) n=94	65 (19) n=89	0.193	4 (-2 to 10)
12 months	65 (20) n=95	67 (18) n=90	0.471	2 (-4 to 8)
Difference at 12m	7 (19) n=95	7 (20) n=90	0.790	1 (-5 to 7)

4.2.3.3 IMPACT

Responses to the Work Productivity and Activity Impairment questionnaire are shown in **Table 4.10**. Half of all participants in each group were not working at randomisation. There were no significant differences in employment between the two participant groups at subsequent follow-ups. In terms of self-reported hours missed from work due to the disease, responses were non-significantly different between the two participant groups at randomisation and at each of the 4 follow-ups, except for that at 12 months. At 12 months, participants in the TLA device group reported having missed 2.1 (S.D. 7.7) hours during the past 7 days as opposed to 4.0 (S.D. 9.3) hours in the placebo group (p=0.049). Regardless of this finding, participants rated the impact of asthma on their ability to work and perform their daily activities similarly across all follow-ups.

Table 4.10 Responses to the Work Productivity and Activity Impairment (WPAI(A)) questionnaire

	Placebo		**Active**		**P Value**
Currently employed, n (%)					
Randomisation	n=117	59 (50)	n=111	59 (53)	0.681
3 months	n=106	54 (51)	n=98	56 (57)	0.375
6 months	n=97	47 (48)	n=95	56 (59)	0.145
9 months	n=93	43 (46)	n=89	49 (55)	0.234
12 months	n=91	48 (53)	n=86	49 (57)	0.572
Hours missed work during past seven days due to asthma, mean (S.D)					
Randomisation	n=55	3.6 (8.7)	n=58	2.2 (5.8)	0.306
3 months	n=54	3.7 (9.5)	n=56	2.4 (9.2)	0.484
6 months	n=47	3.5 (8.9)	n=55	2.1 (7.7)	0.386

9 months	n=43	3.1 (9.2)	n=48	2.1 (5.0)	0.513
12 months	n=49	4.0 (9.3)	n=50	1.1 (4.1)	0.049
Hours missed work during past seven days due to other reasons, mean (S.D)					
Randomisation	n=54	3.4 (13.6)	n=58	2.8 (9.2)	0.779
3 months	n=53	4.2 (9.4)	n=56	4.5 (10.5)	0.867
6 months	n=46	3.3 (12.2)	n=55	2.8 (7.8)	0.807
9 months	n=43	7.0 (27.0)	n=47	3.4 (9.0)	0.393
12 months	n=48	1.5 (5.6)	n=49	0.8 (3.5)	0.436
Hours actually worked during past seven days, mean (S.D).					
Randomisation	n=57	28.3 (16.4)	n=59	31.8 (17.6)	0.270
3 months	n=54	23.9 (18.8)	n=56	28.4 (17.4)	0.190
6 months	n=47	26.9 (19.3)	n=56	30.4 (17.7)	0.350
9 months	n=44	24.8 (18.0)	n=49	30.9 (20.8)	0.133
12 months	n=48	28.8 (18.0)	n=49	31.1 (15.5)	0.506
Impact of asthma on work productivity*, mean (S.D).					
Randomisation	n=61	4.0 (2.8)	n=54	3.4 (2.8)	0.285
3 months	n=51	2.8 (2.8)	n=53	2.8 (2.5)	0.895
6 months	n=50	3.0 (3.0)	n=55	2.7 (2.5)	0.543
9 months	n=43	2.4 (2.5)	n=50	3.4 (3.0)	0.083
12 months	n=47	2.5 (2.7)	n=54	2.7 (2.6)	0.658
Impact of asthma on regular daily activities*, mean (S.D).					
Randomisation	n=116	5.4 (2.4)	n=109	5.0 (2.5)	0.266
3 months	n=105	4.6 (2.9)	n=95	4.1 (2.5)	0.171
6 months	n=93	4.6 (2.9)	n=96	3.9 (2.9)	0.141
9 months	n=89	4.2 (2.9)	n=90	4.1 (2.7)	0.807
12 months	n=90	3.9 (3.0)	n=87	3.9 (2.7)	0.966

*On scale of 0 (asthma had no effect) to 10 (asthma completely prevented work/doing daily activities)

4.2.3.4 TREATMENT EFFECT

Responses to the Global Evaluation of Treatment Effect questionnaire are shown in **Table 4.11**, for over half of all participants there was a perceived improvement in the participant's asthma in both participant groups over the 12 months of the trial. However, regardless of who completed the GETE, either participant or trial physician, there were no statistically significant differences in GETE responses between the two treatment groups.

Table 4.11 Responses to the global evaluation of treatment effect

	Placebo n (%)	**Active** n (%)	**p>|z|**
Completed by trial physician*			
Complete control	1 (3)	1 (3)	0.861
Marked improvement	13 (33)	13 (42)	
Discernible but limited improvement	13 (33)	9 (29)	
No appreciable change	11 (28)	8 (26)	
Worsening	1	0	
Completed by participant, confirmed only†			
Complete control	4 (11)	2 (6)	0.425
Marked improvement	15 (39)	12 (39)	
Discernible but limited improvement	7 (18)	10 (32)	
No appreciable change	12 (32)	6 (19)	
Worsening	0	1 (3)	
Completed by participant, confirmed and possible**			
Complete control	7 (8)	5 (6)	0.347
Marked improvement	34 (38)	33 (38)	
Discernible but limited improvement	22 (24)	32 (37)	
No appreciable change	25 (28)	16 (18)	
Worsening	2 (2)	1 (1)	

*Numbers completing: placebo=39; TLA device=31
†Numbers completing: placebo=38; TLA device=31
**Numbers completing: placebo=90; TLA device=87

4.2.4 SAFETY, HARM AND UNINTENDED EFFECTS

Three participants died during the trial and post-trial period: two during the trial and one after the primary time point at 12 months. The SAE report classification for these deaths is shown in **Table 4.12**.

Table 4.12 Study deaths

Days from Randomisation to death	SAE report classification	Dated severe exacerbations at 1 year	Total Maximum severe exacerbations	Follow up severe exacerbations reported
22	Cardiac event/secondary sepsis	1	1	0
345	Cause unknown	1	3	3
417*	Aortic Aneurysm	0	0	0

* After trial primary endpoint of 365 days

Table 4.13 summarises the AEs and SAEs reported in the sources of primary outcome data (see Section 2.11.2.2 for list) by treatment group, respectively. The protocol did not require asthma exacerbations to be reported separately as SAEs or AEs, so these are excluded from the table.

Table 4.13 Summary of AEs and SAEs Reported

	Serious adverse event			Adverse event		
Event description	**Active**	**Placebo**	**Total**	**Active**	**Placebo**	**Total**
Acute coronary syndrome	.	1	1	.	.	0
Acute pulmonary embolism	.	1	1	.	.	0
Aortic aneurysm	.	1	1	.	.	0
Bronchospasm (following lung function tests)		1	1	1	.	1
Cellulitis	1	1	2	.	3	3
Dental disease	.	.	0	.	1	1
Depression	.	.	0	1	.	1
Dry eyes	.	.	0	.	1	1
Dry mouth	.	.	0	.	1	1
Ear infection	.	.	0	.	1	1
Exacerbation of eczema	.	.	0	.	1	1
Exacerbation of multiple sclerosis	.	.	0	2	.	2
Fall	.	.	0	.	1	1
Fracture (ankle / leg)	1	.	1	.	1	1
Gastroenteritis	1	.	1	.	.	0
Gynaecological symptoms	1	.	1	.	1	1

Headache/migraine	.	1	1	.	4	4
Hip fracture	1	.	1	.	.	0
Hypertension	.	.	0	.	1	1
Hypokalaemia	.	1	1	.	.	0
Ischaemic heart disease	1	.	1	.	.	0
Kidney infection	1	.	1	.	.	0
Lower respiratory tract infection	2	2	4	.	1	1
Musculoskeletal pain	.	.	0	.	2	2
Pneumonia	1	.	1	.	.	0
Post-surgical injury	1	.	1	.	.	0
Sore eye	.	.	0	.	2	2
Sore throat	.	.	0	.	3	3
Stroke	1	.	1	.	.	0
Superficial skin injury	.	.	0	.	1	1
Trauma to toe	.	.	0	.	1	1
Upper GI bleed	1		1	.	.	0
Upper respiratory symptoms	.	.	0	.	1	1
Upper respiratory tract infection	.	.	0	2	.	2
Viral meningitis	1	.	1	.	.	0
Total	**14**	**9**	**23**	**6**	**27**	**33**

Adverse events were similar in both treatment groups and none of the SAEs were device-related following causality assessments. There were five adverse events reported (in four patients) considered to be probably related to the device, all in the placebo group. These included: (i) sore eye thought to be from a piece of the machine's Airshower falling into the eye at night, (ii) grazed back of hand against the machine's Airshower, (iii) sneezing when using the device, (iv) headaches and sore throat, which resolved on stopping device usage.

CHAPTER 5 QUALITATIVE RESULTS

As with any qualitative research it is unlikely that the comments received can be generalised to include all participants in the LASER Trial and users of the TLA treatment device. Nevertheless, the responses received represent a range of participants and describe their experience of using the TLA treatment device.

5.1 SUMMARY OF FOCUS GROUP FINDINGS

5.1.1 DEVICE DELIVERY AND INSTALLATION

During the LASER Trial, delivery and installation of the TLA device to participant's homes was contracted to a logistics company, Bishopsgate, who specialise in the delivery of medical devices.

It was felt important to evaluate participants' experience and the impact of device delivery and installation recognising that the device was installed in the participant's home, in their bedroom, and might require modification of the bedroom environment to accommodate the device.

Participant's experience of the device delivery and installation process was generally positive with most participants reporting that the process was easily arranged and straightforward. The device was set up in the participant's bedroom by the delivery team with the participant and they were then left with clear written instructions.

This was not the case for one participant who was one of the first trial participants; She described the process of device installation being very unprofessional with the delivery team clearly not understanding how the device should be set up. The participant felt that they were a 'guinea pig' for the trial. This incident was highlighted to the trial team at the time and arrangements were made for further training of the delivery team.

Difficulties with device installation will have reflected badly on the trial and may have affected the participant's confidence in the trial and in the treatment being delivered.

Another point that was raised was that delivery was only available during normal working hours meaning that some participants had to take time off work to allow for delivery and installation of the device. These participants highlighted that they already felt under pressure for having to take time off work for hospital appointments and study visits so this requirement to take additional time off was not always welcome.

Most of the focus group participants had had to make minor or major modifications to their bedroom in order to accommodate the treatment device. In most cases this was just removal of a bedside table to allow the device to be installed by the bed. In some cases, more significant moving of furniture and bedroom reconfiguration was required.

The focus group interviews will not have taken into account the views of participants who were unable to accommodate the treatment device in the bedroom as they were excluded from participating in the trial. This must be recognised as a limitation of the treatment.

5.1.2 User Experience

The most important reason for conducting the qualitative, focus group, interviews was to ascertain participant's perceptions of TLA treatment including tolerability of the device and barriers to device use as well as the impact of TLA treatment on the participant.

Participants were asked to comment on both positive and negative feelings towards the treatment device.

With all treatments, both pharmaceutical and non-pharmaceutical, there is an important balance between treatment benefit and the risks of treatment including unwanted side effects. Although TLA treatment delivered by the Airsonett® device has no recognized side effects, unwanted device effects could be considered to be side effects of the treatment.

In our qualitative interviews we identified the main unwanted device effect as noise and most participants commented on the noise of the device. The device is quoted as having a sound level of 38dB, roughly equivalent to a quiet whisper.

Very few participants withdrew from the trial as a result of the device noise but those interviewed in the focus group acknowledged that it took some getting used to. Some participants even went as far as saying that they felt that they liked the noise and missed it when they were not sleeping under the device.

One participant did report that they had come close to withdrawing from the trial as a result of the device noise but had persevered with the treatment. It is important that patients are made aware of the noise generated by the device before having the device installed.

Means of reducing the noise generated by the working mechanism of the device might help improve device acceptability and improve compliance and so this has been fed back to the device manufacturer for consideration.

Qualitative, one to one, telephone interviews conducted during the pilot phase of the trial had raised some concern about smell and heat generated by the device but this did not seem to be a barrier to device use within the group of participants interviewed in the focus groups.

A number of the focus group participants felt that there had been an improvement in their asthma symptoms in the year that they had received the trial treatment, acknowledging that they did not know if they were on an active or placebo device.

One participant reported that whether or not their asthma had improved, their sleep quality had improved during the trial treatment period.

A number of participants highlighted that they had been injured whilst using the TLA device. The Airshower of the TLA device is covered in an abrasive material. Due to it being positioned directly above the participant's head whilst in bed, they reported that there had been occasions when they had sustained minor abrasions when knocking their head or hand on the device whilst getting up or turning over in bed at night. None of those participants that took part in the focus group interviews felt that this was a barrier to the use of the treatment device but this will be reported back to the device manufacturer.

5.1.3 Design Features

In order to inform product development, participants were asked about design features that they felt could be modified or introduced to improve user experience.

The most frequent observation was that the Perspex table which is integral to the treatment device is too small. Most participants had been required to remove a bedside table in order to accommodate the treatment device. They reported that the device was too small to hold what would usually be stored on a bedside table such as a lamp, medications or a drink. Participants were concerned that the device might malfunction if they were to inadvertently spill liquid on to, or in to, the device.

Most participants had a lamp on their bedside table which had also been removed along with the bedside table to accommodate the device. It was suggested that a useful design feature would be an integral light for reading as a substitute for the bedside lamp.

Some participants had problems with the device's power cord. The power cord is inserted under the device. Participants reported that this was difficult to locate and due to the angle of insertion, the cord had a tendency to become dislodged or fall out.

Participants also agreed that a helpful design modification would be to the neck of the device, making it swivel so that the device user could move it out of the way when getting into and out of bed and when making the bed. Currently the neck position is fixed.

Participants also commented on the weight of the device complaining that it was too heavy to move. This was particularly in the context of cleaning the bedroom where they felt that they were unable to clean effectively around the device without being able to move it.

Participants also felt that a lighter, more portable machine might be beneficial so that it could be used in other rooms of the house, for instance whilst watching television.

5.2 Detailed Results Including Verbatim Quotations

5.2.1 Delivery and Installation

Participants were asked about their experience of the installation of the TLA device in their home.

Delivery and installation of the TLA devices was contracted to Bishopsgate, a company specialising in medical device logistics.

Most participants felt that the delivery and installation had been straightforward.

They seemed to be very knowledgeable. I didn't know whether they were just delivery or whether they were...how much knowledge they had but they seemed to be quite knowledgeable. (P2)

They did actually, I've just remembered, they did have a tape measure and take photographs of where my pillow came and they took away a photograph and we were told we couldn't move it from its position. (P6)

[AD And did they set the machine all up for you, did they?]

[General yes].

[AD And did they give you instructions to set them up?]

Yes. (P4)

Yes. (P1)

Clear, clear as mud. (UF)

Yes, yes, very good. (P2)

I thought they worked rather well together, because I work well with my colleagues at work and we know the task to be done and there's no verbal conversation about who's going to do what, someone just gets on and does one task while someone gets on and does the other task…there's no verbal communication; you just do it as a team. And this is what I observed with them, so I was quite enthusiastic. (P10)

[AD So you thought they were competent.]

Yeah, oh yeah, of course. (P10)

I think it's just one young chap on his own at first who installed it, it was just quite straightforward…he was very pleasant. And then when the filter needed to be changed after six months... one chap came…he knew what he was doing. (P7)

Early in the trial, there were some problems with devices being installed incorrectly. This was identified and rectified with further training for the team members who were responsible for the installations.

One of the participants in Focus Group 2 was one of the participants where there was some concern. She reported that the staff did not seem 100% competent. The device was eventually installed

correctly but this did not give a good impression of the trial and may have affected the participant's confidence in the trial and the treatment.

I mean, they were lovely. It was a... they were the delivery chaps and it was a dad and son and they were so bumbly, sort of Stan and Errol, and they put it round the wrong way and so I had a picture of the... we had all the pamphlets and everything, and I said that doesn't look... should it be the other way, and he said oh, give us that picture. And he said, oh yes, I think you're right. And he said he'd been on the course the week before. Now, these are delivery chaps, so they're not [unclear] and they're trying to put it together and so and then they got the tape measure out and the son wasn't doing it right, so dad took over. And it was funny, but it was a bit bumbling... because I was not confident about the two lovely chaps. I read the whole thing in a hurry, read the book of words and how it should be and we all measured it again and...

[AD So in fact it had a positive effect, you took more interest in it, sense of ownership.]

Yeah, in what it was, but I hope that the people that were having it delivered the rest of the time they'd got their act together. (P9)

Yeah, I felt the pilot, the guinea pig. [overtalking] ***he'd never seen it…at least I'd seen what it was supposed to look like. (P9)***

Reassuringly, in that same Focus Group the other participants who entered the trial at a later date reported that they had not had a similar experience.

I don't know if it was the same two chaps that came to me, but they were quite efficient by the time they got to our house…They obviously knew what they were doing by that point. (P8)

I think it's just one young chap on his own at first who installed it, it was just quite straightforward…[unclear] and then put it to the appropriate height…he was very pleasant. (P7)

One participant complained that he had to take time off work for the device to be delivered. He was given a time slot and the device was delivered on time. Many of the participants would have had time off work through illness or to attend hospital appointments and these additional days for delivery of the device and for the filter changes will add up.

I had to have a day off work to wait for the little man to come, two little men…it had to be installed and then we had to be trained up on using it…Which is fine, but I've had a bad year and used up all my holiday…and this was just another one of those things; so that's a downside for me…it's a shame it couldn't just be here are some instructions, assemble it yourself. (P10)

[AD What about an evening, did they offer you an evening?]

I don't recall being offered an evening, it was a nine to five thing, which is time off work.

[AD And no weekends.]

I wasn't offered weekends.

[AD Okay, would that have helped?]

It would've, yeah (P10)

Other participants worked from home so did not find this to be a major inconvenience.

Well, I work from home, so it didn't matter (P8)

No, I mean, I can work from home, so I know the day they gave me... it wasn't tortuous. (P9)

5.2.2 Bedroom Modification

Participants were asked about their experience of having the TLA treatment device in their bedroom. A number of participants reported that they had to make minor modifications to their bedrooms in order to accommodate the TLA device such as removing a bedside table.

I just picked up the bedside table that I had and moved it to a room next door while this thing was put in place; that was the only thing, I had to clear a bit of space for. (P10)

We haven't got a big bedroom and it was just getting things right but we did and it's all worth the effort at the end of the day, very much so. (P2)

Yes I had to shift things around because I've really got a small room because I live back at home with my mum, and me and my boyfriend sleep in there but it's like a box room quite... That's the only thing. (P1)

[AD Right, so you had to do a bit of shifting around to get the machine in there.]

Yes. (P1)

I've just finished with my bedside lamp and my bedside cabinet (P6)

Other participants had to make more significant changes.

We had to swap sides of the bed, which was a bit odd after 20 years…Because it doesn't fit the other side, so because the way the bedroom's laid out with the furniture… you couldn't swap it round because the position of the window and so yeah, that was a bit odd. (P8)

We have a small bedroom and we have individual single beds that were pushed together but now they're apart to get the [device in]... If I was a bit more sensitive and perhaps we'd been married less long I would have said it's come between us…But it's all worthwhile, definitely worthwhile but we did have to do some major upheaval to get everything right in the bedroom. (P2)

One participant was not able to close his bedroom door when the device was in situ. He commented that this was because the device footprint was in a different orientation to his bedside table.

…bedside tables are quite narrow and deep, whereas this machine's the opposite way round and it's so wide that I can't shut the bedroom door…because of where the bed is and the shape of the room I think, I can't shut the bedroom door, which I don't really care about. But when we've got visitors staying my snoring helps keep them awake as well and if we could shut the door it would be slightly better for them. (P10)

5.2.3 User Experience

One of the most important reasons for conducting the Focus Group interviews was to understand participant's perceptions of TLA treatment.

This is important to allow us to identify barriers to treatment adherence and to inform the device manufacturer's product development in order to make the device as user friendly as possible.

5.2.3.1 User Experience - Negative

Device Noise

A number of participants commented on the noise of the device. The device is quoted as having a noise level of 38dB – equivalent to a quiet whisper or a suburban street. Participants are made aware of this in the PIS.

Some found the noise difficult to get used to at first.

…Very difficult to get used to the first few nights. Not much sleep at all. Because it's just constant noise. I was expecting it to be a lot quieter having heard it at the hotel. We just thought there was going to be no noise at all. It's great. But there is noise and it's a lot more than I expected. But you do get used to it. And then, actually, you go somewhere else and you haven't got it and you can't sleep. So it's almost like mood music. You get used to it then you can't live without it. (P1)

I agree. My husband, he's been totally on board with it, no complaints. But we both did struggle to get used to the noise. (P5)

Others had no problem with the noise at all

No problems with the noise whatsoever. (P6)

It was very handy in the morning as I know when to get up. [when the device switched itself off and the noise stopped] (P3)

I had no problems with the noise. (P4)

One participant reported that they had come close to turning the device off due to the noise.

I have come close through not being able to sleep with the noise to turning it off, but haven't, but have come close. (P5)

In total 3 participants withdrew from the trial as a result of not being able to tolerate the noise of the device.

Two of the focus group participants reported that the noise had been a problem for their partners. This is an important consideration as this may also be a reason why some patients might not be able to use the device in future.

My wife…is a bit of a light sleeper, so she's getting a bit grumpified [sic] about the bloody machine… it keeps her awake…the noise when it starts up and the noise when it goes off, it shakes and vibrates a little bit, and the air coming out of the machine.

[AD So that's while it's on all the time, she can hear that continually.]

Yeah. She's got quite delicate hearing. I don't know how with my snoring, but it keeps her awake. And the nearer we're getting to the end of the thing the grumpier she's getting. So I won't be taking up your offer of keeping it.

[AD That's interesting because... not because you...]

No, not because... I'd like to, but it's just too noisy. And it's better to have a patient wife than anything else.

[AD Okay. She didn't make you stop using it at all?]

No.

[AD Well, you can be honest.]

No, because I was saying I've signed up for the study, we've got it for a year, I asked her in advance and you said yes, so it's here for a year; live with it. (P10)

The noise. My boyfriend complains about the noise. It sounds like an aeroplane, he says. But I don't find it that bad but I think other people… I think we're used to it, but they're… yes. (P1)

Smell and Heat

The early trial telephone interviews identified that some participants had noticed that there was a distinctive smell whenever the device was switched on and one participant complained about the heat generated by the device.

Each of the Focus Groups was asked specifically about heat and smell.

One participant in Focus Group 2 reported that she had notice a smell of dust and one participant in the same Focus Group noticed that there was some heat generated by the mechanism of the device.

It does smell, that's why I wonder whether mine's not an actual device because sometimes it smells of dust when it first turns on, so I get the slight odour of dust. (P8)

Mine is hot. (P4)

None of the participants in Focus Group 3 noticed any smell or heat.

[AD Any smell to it?]

[All say ***no***].

[AD Is there any heat from the machine that worries anyone?]

[All say ***no***].

Airshower Injury

A number of participants reported that they had hit their head or hand on the Airshower of the TLA device. The Airshower has a rough surface which is engineered to ensure that the descending laminar airflow is kept separate from the ambient room air.

Due to its position above the patient's pillow, there were occasions when participants hit their head or hand whilst getting in or out of bed. No major injuries were sustained but participants questioned why this was such an abrasive surface.

Hitting your head, even after six months, I'd... you always knew it was there, but just now and again just sitting yourself... sit up or sit down and you know you've got to sort of... round it or cup of tea in bed, I've got my little iPad thing, and just ugh, bang. (P9)

A couple of... a few times. Not too often.

[AD Not enough to say not using this thing again.]

No. (P8)

You learn to not sit up too quick. (P4)

Oh, yes! (P2)

You only do it once or twice don't you? (P5)

Yes. (P4)

[AD How many of you have hit your head?]

[General ***yes***].

Several times. (P4)

[AD Everybody?]

Everybody. (UF)

[Seven of the seven have hit their head. Often?]

No. (P6)

No. (P3)

I don't do it very often. (P1)

It's not noticeable anyway. If you do, it's only plastic. (P3)

I scraped my hand on it a few times. (P1)

Yes I've done that lots of times. (P2)

And it hurt (P6)

It's like pumice stone, scrapes your knuckle. It's a small price to pay. (P5)

Yes, yes, it is. (P4)

If I sit up, my head doesn't touch it. When I knock my head on it is when we're trying to make the bed…But again, a small price to pay. But if I sit up I don't touch it.

It's more if you're leaping out, springing out. So it's not a big issue. (P6)

Weight

A number of participants commented on the weight of the device. This was in the context of when trying to move the device to clean the room.

The device weighs 23kg. Ideally participants are asked not to move the device during the trial. Participants commented that they would like the device to be lighter so that it could be moved more easily and potentially then made portable so that it could be taken away from home when on holiday or spending extended periods away from the home.

It's incredibly heavy…it's got a quite heavy base. I mean, I've put the Hoover edges to it, I do Hoover , I just... but I have trouble...it's not like a chair you can drag and [overtalking]... the base is very heavy. (P9)

I would like a bit more movement underneath so small casters or something. I'm always afraid of moving it too much out of position but it would help if it was a bit easier especially when I'm breathless. (P2)

…you need either lockable wheels because asthma's all about dust and if you can't move it...We were told not to move it at all by the people. We've also got a drawer under the bed which we can't use now but considering asthma's all about dust it needs to be made more easily mobile so you can move it once a week to vacuum under it. I can't move it at all. (P6)

2 participants reported that they didn't try to move the device because they would be concerned that they had not returned it to the correct position,

I think I would be afraid of would I definitely put it back in the right place? (P5)

I haven't actually tried to move mine, so I don't know. (P8)

Use of Fan/Air Conditioning

Participants are asked to avoid using fans or air conditioning units in the room where the device is installed as this would affect the laminar flow of cooled, filtered air. Participants are also asked not to have windows open if possible and if the window is open to ensure that the door is shut to prevent a cross draught from disturbing the laminar airflow.

One participant complained that she had been unable to sleep with a fan on during the trial.

…we can't now have fans on. You can't have any air flow through the bedroom. For me, the biggest problem is I wasn't sleeping… I was so hot, I was absolutely dripping, so I could… I normally have a fan on me all night, and this thing isn't blowing any cold air onto me. And I was just so tired because I was absolutely sweltering. No window open. You're not allowed to have any air flow through. And then no window open and no fan. (P2)

This participant came close to withdrawing from the trial.

I would say nearly switched it off during the summer to have the fan on because I was so hot. (P2)

5.2.3.2 User Experience - Positive

Noise

Although as described above, some participants and their partners found the noise difficult to get used to, a number of participants commented on how they got used to the noise and even missed it when they were away from home.

It's a bit weird the thing on your face initially, but it didn't take long to get used to and I quite like the hum (P8)

You kind of miss it after a while.

[AD Really?]

Yeah, if I had... I rarely but Saturday night, couple of sherries, and it's sparked out. And I wake up about 1:00 and I think what's wrong? Yeah, and it's... apart from him snoring away, I go oh, I haven't turned the stupid thing on…(P9)

One participant reported that her partner quite liked the noise.

I'm ex-Navy and my husband's Navy and it makes us feel like we're on a ship, it's like a [inaudible: laughter] you've got that hum in the background. (P8)

[AD But not the sway.]

Not the sway, if you'd add the sway he'd feel quite at home. (P8)

Improved Sleep

Two participants reported that they felt that their sleep quality had improved.

I'm finding that I'm sleeping much better (P7)

…Once we got over the noise we slept really well and even my husband said we'll keep this machine because we sleep better under it. (P1)

Improved Asthma Symptoms

A number of participants commented on positive treatment effects with a reduction in asthma symptoms and reduced frequency of exacerbations.

I've gone from having four or five exacerbations a year to none. (P6)

I've done my year and I'm into my second year. The first year, it was noticeable, I only had one exacerbation in that year. Just coming down from one at the moment. So it doesn't do away with it all together but mine is infection based as well. That one year, I nearly got away with that one winter of having an infection and getting problems, it was noticeable… it's been a lot… I think it's been marvellous. (P6)

…my cough wasn't nearly so bad after I'd been using it for a while. (P7)

I'm certainly a lot better than I was before the trial started. Whether it's to do with the machine or not, I don't know. But I'm delighted. I have had other problems but certainly my breathing has markedly improved. (P4)

I haven't had to have antibiotics and steroids or anything like that, so that's another plus point. (P10)

And some days I've given got up and gone off to work without having my puffers [reliever inhaler]

[AD Really.]

Yeah. Because I used to have to reach for them when I got up, after being in the bathroom, but I had to have them before I could get dressed and before I could walk the dog and before I could ride my motorbike to work, I'd have to have my puffer. But for the last year or so I haven't needed it. (P10)

This wasn't the case with all participants.

I'm not too sure. I've had a few exacerbations; I've been in hospital, I think, beginning of November and I'm on steroids at the moment now. So I am not too good at the moment. I can breathe a bit better but I've been off work this week.

[AD So for you you're not sure if it is the machine.]

I'm happy to take part though, I think it'll be useful, hopefully. (P1)

One participant who has now completed the trial and is using an active treatment device in the post-trial provision period felt that she might have been on a placebo device as her symptoms had improved since finishing the trial.

Knowing that I'm on the real one and have been for six months, I feel that... I do feel the benefits…I was very ill during my time, my year with it…so I think I had the placebo, because now having had six months of the real thing, I can tell the difference. (P9)

Partner Benefits

Interestingly one participant felt that perhaps the TLA treatment might be having a beneficial effect in reducing her husband's snoring.

I have to say, I think he got a bit quieter, I wondered if he was benefiting from it. I don't... you know (P9)

5.2.4 Design Features

Participants were asked to comment on any issues they found with using the device and any design modifications that they might recommend for future product development in order to make the device more user friendly.

A number of participants commented on the Perspex shelf/table that is provided with the device. As described above, the device often replaces a bedside table and so participants felt that this should be able to accommodate what would usually be stored on a bedside table.

…a better table attachment, because it replaced the bedside table and there's not a lot of space, I read a lot of books, there's a lot of books. It would be helpful to have something you felt confident putting your glass of water on, which I don't put my glass of water on it…If it falls into the device, then what, it's not going to be ideal.

[AD And would you normally have your bedside light on that table, so you had to compromise, did you?]

Yeah. (P8)

It's quite sturdy, isn't it, it seems to be... because it's Perspex, it looks a bit... so I was hesitant to put a coffee or a water on it, but it's stronger... I think it's stronger than it looks. (P9)

[AD Right, but not big enough perhaps for what you really wanted.]

Yeah, it's a small area, it's more my concern about trashing it, I suppose. (P8)

[AD And then the table, you're not keen on the table, the little table?]

Not much. (P3)

Well, it's useful. (P2)

Better than nothing. I had to lose the bedside cabinet, but it was better than nothing. (P5)

I had to lose my bedside cabinet and there's nowhere to put my coffee. (UF)

[AD Are you worried about where you put your coffee?]

I wouldn't put coffee on anything…(UF)

It's not quite flat. It's always slightly…(P3)

What I do at night is take a bottle of water up with a lid on it. I don't have a glass of water. (P2)

I have a sports bottle. (P5)

Yes, me too, so there's no chance of spilling. (P2)

[AD But can you get a bedside table, a lamp on it?]

No. (UF)

No. (UF)

[AD It's just your clock, is it?]

Not only that, it's the wrong size, it doesn't cast a light. (P4)

I have my contact lenses and my inhaler and that's it. (P3)

One participant commented on the socket for the mains electrical lead to the device. This is positioned in an awkward location under the device and in a position that would be difficult to access when the device is in situ. He had noticed that his device had stopped working and eventually found it to be due to the plug having become disconnected for the device.

Other participants agreed that this was a problem.

I thought it was broken for a while, it seemed dead, but because the power cord goes up into the bottom, I'd actually left the power cord in and it fell out. You switch it on at the wall. But I must have moved it somehow and the power cord just fell out the bottom because it goes in upwards. (P3)

Yes, it is really difficult to find (UF) [overtalking].

I hadn't even noticed it but once I saw that, it was about six or seven days, and once I plugged it back in I felt silly as well. (P3)

Yes. Actually, I found that plug very difficult to cope with because you've got to go down on your hands and knees. (P2)

[Others agree it is difficult].

Two participants talked about the positioning of the device in relation to the bed.

One participant thought that the device would be better positioned at the head of the bed.

I wouldn't have thought it wouldn't be that difficult to get it to go behind the bed instead of at the side of the bed, probably redesign the machine to some extent. We can pull the bed out that way but this side is not functional. (P4)

The other participant questioned whether the main body of the device could be positioned under the bed, out of the way.

For me, design-wise, I mean I know everyone's bed is different, you have divans or whatever, but the bit at the back, if they could somehow encompass it so you can have a different model that's got a lot of workings that go under the bed. So you push it like a forklift truck under the bed…Because the back bit is the bulky bit. And that's why you have to get rid of your bedside cabinets. (P3)

A common and popular suggestion was that perhaps the neck of the device and the Airshower could be adjustable for ease of positioning and on a swivel so that it could be moved out of the way of the bed when getting in and out of bed and when making the bed.

An arm that swivels round so you could get up and sit back (P9)

So if this was on a swivel and you wanted to sit in bed, you could just swivel it out the way and sit in bed…But as it is it's fixed.

[AD Right, so you have to get in and get under it.]

If you was an old person I doubt whether you could just pick it up and move it. (P10)

One participant commented on how he was required to re-programme his device following a power-cut. He thought that there should a memory capacity so that this was not required each time the mains power was switched off. This would seem like a good idea.

…when we had a power cut we... someone had to programme in the times again, because it seemed to erase its memory for some reason.

[AD Right, easy to do?]

I thought it would've had a little bios battery in there that stored everything.

[AD So it all went blank and you had to...]

Yeah, I had to put the date and the time in. (P10)

As a result of having to replace her bedside table with the treatment device, one participant no longer had a bedside light. She suggested that a future design might incorporate a light into the device.

I've got no light by my bedside table now. So if I wake up during the night and I need my tablets, I am having to feel for them and end up dropping them on the floor. They couldn't encompass just some sort of light in the bit that goes up like that, or somewhere where you could somehow click.

Or just say a moulded bit that you could then clip the light onto somehow. I don't read at night but if you read at night it would be very awkward. (P2)

One participant felt that it was important that future models were smaller and more portable so that the treatment could be used when away from the home.

Is there any chance that they will invent something which is more portable?

[AD …Something more portable so you can have it when you're away.]

Yes, for people who are working it probably would be nice for them to have a session in their lunch break.

[AD So a mini version of it.]

Yes. (P6)

Finally, one participant thought the device should come equipped with a minibar!

Minibar [overtalking]***. A table for the minibar. (P9)***

Table 5.1: Key to Verbatim Quotation Contributors

P1-10:	Participants 1-10
UF:	Unidentified Female – voice not recognised in digital transcription
AD:	Dr Ann Dewey – Senior Qualitative Researcher and Facilitator

CHAPTER 6 DISCUSSION AND CONCLUSION

6.1 DISCUSSION

The LASER Trial has found that, in the population of patients with severe, exacerbation prone, allergic asthma randomised to treatment, the addition of a TLA device to standard medical care resulted in no statistically or clinically significant benefit in reducing the frequency of severe exacerbations.

Although there were no significant differences in the secondary outcomes for spirometric lung function (pre- or post-bronchodilator FEV_1), asthma control or eosinophilic airway inflammation (F_ENO), there was a significant improvement in mean daily PEF in favour of the TLA device. In the light of a lack of improvement in other parameters of lung function, this improvement needs cautious interpretation, although the levels of improved PEF are in the order of expected reductions in peak flow during exacerbations in this patient group.

Use of the TLA device yielded higher levels of generic and disease-specific health-related quality of life with results showing statistically significant higher quality of life at some intermediary follow-up visits.

There were no significant safety concerns between groups and adverse events were similar between the participant groups.

The different outcomes in this Trial compared to previous TLA studies and other anti-allergy interventions in this patient group requires interpretation and this is discussed here in more detail.

6.1.1 ASSESSMENT OF EXACERBATIONS

Frequency of severe exacerbations was chosen as the primary outcome in the LASER Trial for a number of reasons. A significant proportion of the cost of managing asthma derives from the use of acute and unscheduled care for the management of severe exacerbations. As determined by our PPI representatives, asthma exacerbations are also important to patients as they have such an impact on patients' quality of life and their ability to work/study.

Our definition of a severe asthma exacerbation was accurately described and consistent with international trial endpoint criteria. For the purposes of the LASER Trial we chose a threshold of ≥30mgs of Prednisolone or equivalent corticosteroid as it is consistent with the BTS/SIGN guidance for the treatment of severe acute asthma. A post-hoc analysis using a less stringent definition for an exacerbation, an increase in Prednisolone dose of ≥10mgs over baseline dose, showed the same results with no significant reduction in exacerbation frequency.

We had sought to ensure we collected severe exacerbation data from multiple sources to avoid under-reporting and attempted to provide some clinical if not data corroboration that a severe exacerbation had occurred. By attempting to capture more information we unfortunately also increased the potential risk of missing data.

We examined several sources of exacerbation data including the daily TLA diary (TLA) filled out continuously during the trial with a daily corticosteroid dose, the Patient Exacerbation Diary (PED) filled out only during severe exacerbations and Exacerbation Review Forms (REV) completed by the clinical team when the patient reported a severe exacerbation. We had specified in the Trial protocol that asthma exacerbations requiring hospitalisation did not need to be reported as Serious Adverse Events (SAEs) to prevent duplication because this exacerbation data was being collected elsewhere but some of our trial centres still reported them as SAEs. Furthermore, to ensure severe asthma exacerbations were reported even if they had not been recorded in the TLA, PED, REV or SAE, participants were asked to recall the number hospital admissions for asthma exacerbations (HOSP) and total number of severe exacerbations (FU) that they had experienced in the preceding 3 months at each of their follow-up visits (at 3, 6, 9 and 12 months), these were recorded as follow-up exacerbation data.

As we would expect in a real-world RCT, data completion across all formats was not consistent. Many participants completed their daily TLA diaries, others did not, with occasional advice from clinical teams that if they were unable to do so that they at least fill out their PED and/or come for an exacerbation review visit for completion of a REV form when exacerbating. We thus cleaned and matched all the different sources of exacerbation data by date to avoid double counting e.g. courses of oral corticosteroids that coincided with a hospitalisation. We also combined the TLA Diary and PED by date and dose as there were some where the data was incomplete e.g. the date of commencement was offset by a few days, in order to create a combined T/P source of exacerbation.

The consequence of all this is that the number of trial-end point severe exacerbations may not be the same as the sum of the number of severe exacerbations reported by the participants at the follow-up visits, as mild or moderate exacerbations that did not meet the strict trial definition may also have been recalled and reported at these follow-up visits.

We sought to examine all possible measures of severe exacerbations but decided to use only the 344 dated exacerbations in the primary analysis. By using dated exacerbations there was certainty of the data and clinical evidence of oral corticosteroid use to meet our protocol definition. Using this method, we had to assume that where there was missing TLA or PED corticosteroid dose data that patients were not taking oral corticosteroids and therefore did not have a severe exacerbation. This may potentially have led to severe exacerbations being missed.

Using either the reported FU exacerbations or a combination of the dated exacerbations and reported FU exacerbations would allow inclusion of more exacerbations but these two methods would both be subject to recall bias as we could not be certain that participants did not include non-protocol, mild or moderate, exacerbations in their reported FU exacerbations. Examining the reported FU exacerbation responses, it was evident that some participants either under-reported or over-reported exacerbations over and above their dated severe 0exacerbations. Surprisingly, there was evidence of over-reporting of severe exacerbations even by some participants who filled out their TLA diary fully. Another disadvantage of using the reported FU exacerbations is that it would not allow for those who under-reported on FU exacerbations if we had evidence of more exacerbations from dated severe exacerbation sources. Another problem with the use of reported FU exacerbations is that we would not be able to ascertain whether participants contravened the 7-day rule for separating exacerbations which could potentially allow for over-reporting of exacerbations by participants reporting one exacerbation as two or even more separate exacerbations.

We have also considered the impact of missing TLA diary data on the primary outcome of the rate of severe asthma exacerbation events. The missing data on the TLA diary relates to the failure to record any value (diary entry left blank), and the majority are due to a failure to record a value of zero where likely no exacerbation occurred. Where participants were taking oral corticosteroids at levels of the protocol definition of an exacerbation (≥30 mgs), the proportion where a value had to be assumed as zero in the TLA diary was small, and where the doses of oral corticosteroids were much lower than the protocol definition (<30 mgs) then the proportion of values having to be assumed to be zero was much larger. This indicated that participants were less likely to record lower doses of oral corticosteroids, when for example on maintenance oral corticosteroids or when tapering off from prolonged courses, or recording as zero when they were not taking any and so not in exacerbation (the commonest occurrence). While we had not sought to determine the severity and duration of exacerbations other than their frequency for our primary analysis, this approach may have led to underestimating the rate of events, as we did not have the number of days participants were “at-risk” for the denominator in the model, and we had to assume all days (where there was no value recorded in the TLA) to be considered at risk. The amount of potential missing data according to the TLA diary was potentially significant and could have caused a type 2 error for the primary outcome, i.e., a treatment benefit is not shown even if such an effect existed.

Ultimately, despite merging all available records to provide an integrated record of the number of exacerbations per participant, we were not able to demonstrate a difference in frequency of exacerbations between groups.

6.1.2 Appropriateness of Patient Population and Minimisation

There was a remarkable reduction (approximately 50%) in exacerbation frequency in both groups from baseline to completion of the Trial, but no difference between groups. Across the two groups, 43% of participants reported no exacerbations during the 12-month trial having had at least two exacerbations in the preceding year. This phenomenon of improvement in outcomes under study conditions has been reported in other diseases as well as previously in asthma, and is not explicable simply by a regression to the mean effect; we would have expected that not to have occurred in a year-long study.

The placebo effect in asthma is well recognised but poorly understood (Dutile et al 2014) and needs to be taken into consideration when designing clinical trials. Inclusion of a 'no treatment' arm in the trial is one possibility but there is also evidence of improvement in these groups as well under study conditions (Hróbjartsson et al 2010).

It must be considered that there may be an additional unknown factor or treatment effect related to the treatment device that contributed to the significant improvement in both the active and placebo arms of the trial. One possibility is that this may have resulted from improved sleep quality. Several observational studies have shown a relationship between atopic diseases, including asthma, and sleep disturbance. This relationship is interesting and there is a suggestion that they are interrelated, with either condition being a risk factor for the other (Jernelöv et al 2013). The qualitative focus groups identified that a number of respondents felt that their sleep quality had improved as a result of the device use although it is unclear whether these participants were in the active or placebo arm of the trial. Improvement in sleep quality may or may not have been related to the treatment delivered as it could equally be related to the noise of the device or another unknown factor. Improved sleep quality may have had a positive outcome on asthma control and may help explain the improvement in exacerbation frequency in both treatment arms in the trial.

Other possible explanations for the improvement seen in both treatment groups during the LASER Trial include the improved adherence with treatment under study conditions and the support gained from regular visits and access to healthcare professionals from the site trial teams. We recruited a number of participants into the trial who may not have previously been known to the recruiting site (incident cases) and so the opportunity to correct for factors that might have been driving poor asthma control may have been missed prior to enrolment and become evident during the trial. The risk of this impacting on trial outcome was reduced by including the origin of the case (prevalent or incident case) as a minimisation factor.

It is remarkable that 4 participants in the placebo group recorded a prior exacerbation frequency of 14, 18, 20 and 25 exacerbations in the year prior to participation in the trial. The impact of this was however reduced by including the exacerbation frequency in the previous 12 months (2, 3, ≥3) as a

minimisation factor, and further analysis of the dated exacerbations during the trial shows that there were no participants with skewed exacerbation frequency between the groups.

Although not presented here, we measured the number of hours that the device was used by each participant. The majority of participants possessed a device for more than 6 months of the trial, making them eligible to benefit from the four years' post-trial provision of an active TLA device free of charge. This incentive may have helped with participant retention but this is not a perfect indicator of adherence as even measured hours is not representative of the time spent under the device as the device is pre-programmed to automatically switch on and turn off. Nevertheless, the TLA diaries which asked participants to record their use of the device suggested that, where it was recorded, most participants used the device for sufficient hours to include overnight sleep (8 or more hours). There were instances when participants were on holiday or abroad and in this pragmatic trial we allowed them to continue participation in the trial as long as this meant they spent no longer than a week without the device.

6.1.3 Trial Conduct

All trial centres had a face-to-face site initiation by the Trial Coordinator to ensure all trial procedures were followed. Despite this, 12 incidents of admission to hospital due to exacerbation were identified from SAE reporting (with or without other acute comorbidities); these were re-framed as data contributing to the primary outcome rather than reportable adverse events.

Some site trial teams recognised the onerous nature of the TLA diaries and this may explain why some participants were less likely to record values of zero when well, and why often only PED were completed with accompanying REV. Earlier data quality checks at sites may potentially have identified this problem earlier and reduced the amount of missing data.

6.1.4 Multiple Comparisons

We had considered carefully in the statistical analysis plan that multiple comparisons of the secondary outcome variables would be made, even though these were important to assess and were agreed a priori. We anticipated the possibilities of a Type I error (finding of 'false significance') and had designed the Trial specifically to reduce the chances of such findings. We have conducted a prospective study with adequate power to test our hypothesis, exacerbations were confirmed from multiple sources wherever possible by the research team, we estimated secondary outcome measures objectively by questionnaires and lung function, and we ensured adherence to TLA treatment or placebo as much as was possible

We also anticipated the potential of Type II errors which are no less important than Type I. We believe that even if appropriate, while adjustments for the p-value could reduce Type I errors (which we have done already by other steps outlined above), such a step would

potentially increase the chances of making Type II errors and increase the possibility that important relationships between TLA treatment and asthma symptoms and lung function would not be discovered (Perneger 1998). We had considered the potential adjustment of the p-value at the outset but recognised that such a calculation would have been arbitrary and variable. For example, there would be uncertainty about the number of variables to adjust for. If we had lowered the alpha level and maintained the beta level in the design phase of our study, this would have also greatly increased the sample size required (Rothman 1990), and we consider that such a financial burden would have meant this type of study would have been unlikely to have ever been conducted.

Finally, as we found no consistent and significant effects of TLA treatment in the secondary outcomes, we did not pursue any corrections for multiple comparisons but had considered their potential impact at the outset of the Trial design.

6.1.5 Comparison with other evidence of the TLA device

A larger placebo-controlled trial of the TLA device (Boyle et al 2012) had previously shown an improvement in asthma-related quality of life and reduction in exhaled nitric oxide, with a greater benefit shown in patients with severe asthma (GINA Step 4) and with poor control. That trial was however in a heterogeneous group of asthmatics (age range 7-70 years) randomised 2:1 active to placebo and about half or just less had GINA Step 4 severity of asthma, meaning that the event rate of exacerbations was low. Consequently, despite adequate numbers of participants, the trial was unable to show a reduction in exacerbation frequency. In our trial with a higher proportion of people with severe asthma, we were able to demonstrate improvements in both generic and asthma-related quality of life.

In another, smaller open-labelled study of the TLA device (Schauer et al 2015), in which the participant population was more severely exacerbation-prone than that of our trial (33% were on maintenance oral corticosteroids and 43% were on Omalizumab treatment at baseline, i.e., significant number of BTS Step 5 participants), TLA treatment was found to reduce exacerbation rate from 3.6/year to 1.3/year – a 64% reduction. That study differed from ours in that participants were their “own control” rather than a placebo group, and it included 50% children with an even gender distribution. We report a similar reduction in exacerbation frequency before and after the trial in both groups, but with a female and obese predominant allergic asthma population reflective of ‘real-world’ severe asthma patients.

We have confirmed benefits of improved quality of life in keeping with other evidence, but not in reducing eosinophilic inflammation or exacerbations. We have not tested on systemic effects of allergy, though there were improvements in the sino-nasal scores in favour of the active device

(comparable to the minimally important difference of the SNOT-22 questionnaire) but this was not statistically significant in this population (p=0.07).

6.1.6 Allergic asthma and Its Link With Symptoms

It is plausible that a proportion of severe asthma cases attributable to allergy may be overestimated and that aetiological mechanisms other than allergy may be important in the pathogenesis of severe asthma. For instance, numerous studies have reported a strong association between asthma exacerbations and respiratory viral infections suggesting a viral-induced mechanism (Holt et al 2012). Rather than being mutually exclusive, viruses and allergens may interact in increasing the risk of severe asthma and exacerbation frequency (Green et al Lancet 2002). It is not possible from the data obtained in the LASER trial to determine the aetiological mechanisms of each individual exacerbation and whether other factors were playing a role in the reported exacerbations. A better understanding of the aetiology of specific exacerbations may have demonstrated a different outcome in the trial.

Consistent with European standards (Heinzerling et al 2013), allergic sensitisation was defined in the LASER trial as either an allergen specific serum IgE detected >0.35 KU/l, or a positive skin prick test (SPT) to a defined allergen with a mean wheal diameter of ≥3 mm. These allergy tests have high sensitivity, but in themselves do not necessarily signify disease. A considerable proportion of non-asthmatic individuals are sensitised to one or more aeroallergens and a positive test in an asthmatic patient does not always result in clinical response upon exposure to that allergen. There is a difference between allergic asthma with asthma symptoms induced by exposure to a defined allergen, and asthma in a subject characterized as being sensitised but with no relation between allergen exposure and clinical reaction. In the LASER trial we attempted to overcome this issue by recording both allergen sensitisation by either skin prick testing or measurement of serum specific IgE levels as well as documenting evidence of presence of symptoms on exposure to allergens to which the subject was sensitised. This is imprecise as it relies on subjective reporting of symptoms on exposure to allergens and may have led to the inclusion of participants who did not have purely allergic asthma.

Exacerbations and symptoms often coexist but are not always interlinked. Some patients have significant daily symptoms and require high intensity treatment to maintain quality of life and prevent deterioration in lung function but do not experience frequent exacerbations. It is also recognised that there is an asthmatic phenotype characterised by development of sudden severe asthma symptoms and exacerbations in otherwise mild or asymptomatic subjects, often triggered by exposure to an allergen, a drug, an air pollutant or volatile organic compound, a viral infection or another unknown trigger.

The huge heterogeneity in asthma highlights the importance of characterising specific asthma phenotypes aiming to provide precision therapeutics targeted towards each individual's disease.

Sub-group analysis of trial populations might help to identify specific phenotypes or sub-groups of allergic asthmatic patients who might benefit from specific treatments such as Temperature-controlled Laminar Airflow.

6.1.7 Dissociation Between Asthma Symptoms and Exacerbations

There is good evidence from previous landmark asthma studies showing that there is a dissociation between asthma symptoms and exacerbations.

Early studies investigating the safety and efficacy of mepolizumab (Nucala®, GlaxoSmithKline, London, UK) showed no clinical safety concerns but equally were unable to demonstrate efficacy in the measured primary outcomes. In a double blind placebo controlled study of 24 mild allergic asthmatic patients (Leckie et al 2000), researchers were unable to demonstrate any significant improvement in airway hyper-reactivity, peak expiratory flow or FEV1 in the group treated with mepolizumab compared to placebo despite seeing a significant reduction in airway and blood eosinophil counts in the mepolizumab treated group. A further double blind placebo controlled study (Flood-Page et al 2003) randomised 24 participants to mepolizumab or placebo. Again, researchers were unable to demonstrate any improvement in their clinical endpoints of FEV1, PEF or airway hyper-reactivity despite again showing a significant reduction in blood and airway eosinophils in the active treatment group. Flood-Page et al went on to perform a large multicentre randomised controlled trial in 362 asthma patients with persistent symptoms (Flood-Page et al 2007). Again they were unable to demonstrate significant clinical improvements in symptoms, lung function measures or quality of life in the active treatment group.

Phase II and III studies of mepolizumab treatment in carefully selected populations of severe eosinophilic asthmatic patients were later able to demonstrate a significant reduction in the annualised asthma exacerbation rate despite not showing consistent improvements in asthma symptoms or quality of life measures. The DREAM (Dose Ranging Efficacy And safety with mepolizumab) trial (Pavord et al 2012) treated 621 patients with IV Mepolizumab for 52 weeks. There was a significant reduction in exacerbation rate in the mepolizumab treated participants compared with placebo. It was noted that the significant reduction in exacerbation risk was only associated with small and not clinically significant improvement in measures of asthma symptoms, asthma control, lung function or quality of life.

The SIROCCO study group (Bleeker et al 2016) investigating the anti-IL5 antibody, benralizumab (Fasenra™, AstraZeneca, London, UK), were able to show a similar treatment benefit in reducing the annualised exacerbation rate and were able to show an improvement in FEV1 in the active

treatment group but again could not demonstrate a consistent improvement in asthma symptoms in the active treatment group.

These studies suggest dissociation between symptoms and risk of exacerbation in patients with severe asthma. This evidence is further supported by studies performed to reduce eosinophilic airways inflammation (Green et al BMJ 2002). Green et al were able to show that treatment strategies aimed at normalising sputum eosinophil counts were able to reduce asthma exacerbations and hospital admissions. Despite the significant reduction in exacerbation rate in the sputum management group, the group were unable to demonstrate any improvement in symptom scores, quality of life or lung function measures.

Previous trials of Temperature-controlled Laminar Airflow treatment in asthma have demonstrated improvements in asthma quality of life and, recognising the dissociation between symptoms, quality of life and exacerbations in severe asthma, it may be that further studies to demonstrate efficacy of TLA treatment should focus on symptom control and quality of life given the lack of demonstrable improvement in exacerbation reduction seen in the LASER trial.

6.1.8 Device Compliance

It is important to recognise the difficulty of managing device compliance and adherence. During the LASER trial, participants were asked to commit to using the device on at least 5 of 7 nights of the week, excluding holidays, recognising that this was a pragmatic trial and that the device was not sufficiently portable to allow participants to take on holiday or away from home. Participants were encouraged to use the device every day if possible and to ensure that the device was switched on when sleeping under the device at night.

In order to try and capture a measure of device compliance, participants were asked to record their use of the device on the daily TLA diary including whether the device was used, yes or no, and the number of hours the device was used. In addition to this, participants were asked to report the 'device-reported use'. The device automatically recorded the number of hours 'in-use' when the device was switched on.

The device was pre-programmed at the time of installation by the engineer to turn on and switch off at times defined by the individual participant to cover the 'earliest possible time to bed' and 'latest possible time to rise'. Participants were able to over-ride this function and could turn on the device earlier than programmed and switch off the device earlier than programmed. This also gave participants flexibility to use the device during daytime naps if they wished.

Unfortunately, it is not possible to determine from the device reported use whether the participant was sleeping under the device during the time that the device was switched on.

Difficulties in measuring device compliance mean that it is not possible to absolutely confirm that each participant used the device for a satisfactory length of time to receive a treatment benefit.

Indeed it is not known what length of time a participant would be required to sleep under the device to obtain a positive treatment effect. It would be important in future studies of TLA treatment to have a more robust measure of treatment compliance to allow further analysis of treatment outcome determined by compliance.

6.1.9 Device Acceptability

Through qualitative analysis we found that TLA treatment delivered by the Airsonett® device is acceptable to patients with severe allergic asthma. There were few barriers to treatment use, none of which were insurmountable in our interviewed population.

A number of suggested device modifications have been identified and passed on to the device manufacturer. The device manufacturer was grateful to receive this information to help with their product development and have agreed to keep us informed of future design modifications that stem from this research.

6.1.10 Novel Methods of Recruitment including Social Media

We have been able to explore the benefits of using different social media platforms to recruit and randomise participants. Of 240 randomised, approximately 20% of participants were from sources other than clinic registers at participating centres. Furthermore, fewer than 1% were from newspaper and radio advertisement, which are more traditional methods of recruitment, but no less costly. We demonstrated that use of dedicated trial websites, Google re-marketing, targeted Facebook advertisements and national charity Facebook and Twitter use can enhance recruitment. The most successful was however the use of Trialbee, a dedicated website used for directing participants after a short screening questionnaire to the relevant and local trial sites.

This strategy for recruiting trial participants was considered to be especially appropriate for the trial population, who tend to be younger patients and therefore likely to be working and with less time to engage with the traditional advertising and recruitment pathways, but who are likely to explore the availability of new treatments and technologies for their condition via the internet and social media platforms. Another benefit of social media engagement is that it empowers people to approach the research team of their own volition, thus possibly selecting more motivated, engaged research participants.

Further exploration of the use of digital and social media for recruitment to large multi-centre trials is needed.

6.1.11 Future Work

Previous studies have shown a beneficial effect of TLA treatment in a more heterogeneous and less severe population of allergic asthmatics. There may be a more significant benefit in these less severe patients particularly in terms of improvement in quality of life. The type of patients who may benefit from the TLA treatment requires further exploration.

Exploratory sub-group analysis of the LASER trial data would be helpful to determine whether there is a sub-group of severe allergic asthmatic patients who might benefit from TLA treatment although any sub-group analysis would be under-powered. Suggested analysis of interest would include sub-groups based on gender, BMI, asthma severity, asthma control (ACQ) level and allergen sensitivity.

Of particular interest would be sub-group analysis for specific allergen sensitivity. There may be a more significant response in patients who are sensitised to a specific allergen or those who are sensitised to more than one allergen. Sub-group analysis of patients who use additional allergen interventions such as dust mite prevention pillow and duvet covers would also be of interest.

The reason for the large reduction in exacerbation frequency in both the active and placebo groups in the LASER trial and other severe asthma trials requires further exploration.

Future trials in severe asthma measuring exacerbations as the primary endpoint should include a more robust means of collecting data and it would be recommended that electronic diary collection of daily corticosteroid use and asthma symptoms is used. This is more common in pharmaceutical company sponsored trials where funding is available.

Further qualitative studies should be conducted outside of the trial setting where users of the device can also discuss the clinical benefits of using the device, weighing against the impact of having the treatment device installed at home. This was not possible in this study due to participants being blinded to treatment allocation.

Qualitative analysis of device use in a wider asthma population including patients with less severe disease would be helpful to determine if the device is acceptable in a less severe asthmatic population.

A qualitative analysis of the impact of the treatment device on patient's partners who share the same bedroom environment as the patient using the treatment device would be useful to establish whether this might prove to be a barrier to device use.

6.1.12 Reflections on coordinating a multicentre trial

Reflecting on my role as trial coordinator for the LASER trial I found delivery of a national, multi-centre, trial to be both extremely challenging as well as highly rewarding. Through being directly involved in all aspects of trial delivery from concept and trial design to recruitment and data analysis and interpretation I have learnt a huge amount about successful delivery of both quantitative and qualitative research which I will use to good effect in delivery of my future clinical research.

There are a number of areas that I found particularly rewarding, most notably working with such a highly motivated group of researchers and patients.

I developed excellent working relationships with the other members of the trial management group who were equally motivated to deliver a successful trial. We held regular, weekly meetings to ensure that the trial continued to drive forwards and to make sure that problems and challenges were addressed in a timely manner.

I enjoyed collaborating with patients to better understand their needs and to ensure that the trial was answering a clinically meaningful question. We designed a pragmatic trial to ensure that results would be applicable to a 'real-world' population of severe asthmatic patients. Our PPI members contributed at a number of key stages of the trial. Their input was invaluable at the stage of protocol development ensuring that the trial processes would not put undue burden on participants. PPI representatives also reviewed all patient facing documents to ensure that they were easily understood and met the needs of the trial participants.

I arranged a number of meetings with our recruiting centre trial teams during the course of the trial, both before and during the recruitment phase, to share experiences and troubleshoot problems that were occurring. As trial coordinator this offered me the opportunity to build relationships with the research teams to ensure that they felt supported and able to contact me for advice about any aspect of trial delivery. This was particularly important with trial recruitment and close engagement with site teams allowed us to share good practices. Travelling to trial centres as well as bringing trial teams together at investigator meetings undoubtedly led to the successful recruitment to time and target.

Maintaining good lines of communication with all members of the trial team is crucial to the successful delivery of a national, multicentre trial.

I developed the trial website (www.lasertrial.co.uk) in collaboration with a web developer. This provided a valuable means of communicating the aims and objectives of the trial and provided a source of information for both trial participants and research teams looking to find out more information about TLA treatment and the trial. The trial website also provided a focus for recruitment with trial advertising directing potential participants to a webpage where they were

able to register their interest in the trial. This proved to be a valuable means of recruiting participants who might not have otherwise been able to access the trial.

Alongside the website, I also set-up social media accounts for the trial to engage with patients and make the trial more accessible. These social media accounts linked to the trial website and to national charities applicable to our patient population. Patients and potential participants were able to engage with the trial team through social media and it was clear that through social media interactions, the trial was made available to a wider population than would have been able to access the trial had it only been advertised through trial centres and conventional means.

With the challenges faced by trials to deliver to time and target it is key that efforts are made to engage with patients. In our experience the trial website and utilisation of social media helped to ensure that we were able to meet our targets and we would encourage others to consider using these tools to enhance trial engagement and recruitment.

There were significant logistical difficulties to overcome in the LASER trial most notably with delivery of the trial treatment devices into participant's homes after randomisation. I had long and detailed discussions with the device manufacturer and the logistics company contracted to arrange delivery of the devices and arrange filter changes. We put together a standard operating procedure including a detailed checklist to ensure that the same process was followed in each case. I put together a basic GCP training presentation for the Engineers from the logistics company to make sure that they understood the importance of maintaining blinding when installing the devices and not discussing possible treatment allocation with participants. Even despite these efforts there were situations where the device was installed incorrectly or the participant was unable to arrange a convenient time for the device to be delivered. These situations required prompt action to prevent impact on trial integrity and results.

Early on in the trial we had problems with a number of the trial electronic peak flow devices failing. We made a decision to withdraw all of the allocated devices. I sourced an alternative electronic peak flow device from a different manufacturer. I arranged collection of the old devices and distribution of the new devices to our trial teams. This had to be arranged within a short time period to ensure that we were able to continue recruiting participants and collecting data. As a specific electronic peak flow device had been mentioned in the trial protocol this required an urgent ethics amendment to allow the use of an alternative device.

When we discovered that we were not meeting our recruitment targets I realised that we needed to make changes to ensure that the trial did not fail. Working with the trial management group we proposed a number of protocol amendments that would enhance recruitment without damaging the trial's integrity. We proposed these changes to the trial steering committee who approved and

supported the proposal. I approached the trial ethics committee and 3 major amendments were made to the protocol.

It is important to be flexible and responsive to challenges in order to keep a trial moving in a positive direction.

Missing data was a significant problem in the trial. Attempts were made to review data completeness during the 4-month internal pilot study so that measures could be taken if problems were arising. Unfortunately, data completeness was not raised as a concern by the data management team and when it came to the end of the trial we were faced with a number of missing data points most notably in the daily diary collection of symptoms and daily corticosteroid dose. This had an impact on data interpretation. We reflected that we could have used an electronic diary to collect this data which may have improved data collection or certainly flagged up missing data sooner. The use of electronic diaries would not have been financially viable within the constraints of the trial budget. Budgeting for electronic diary use should be considered by trial teams designing future trials where daily data collection is required.

Every effort should be made to minimise missing data. Robust means of identifying missing data should be put in place so that action can be taken early to avoid problems associated with incomplete data. If necessary, additional training could be delivered to trial teams to highlight data points that are commonly missed.

6.2 CONCLUSION

Despite evidence of the efficacy of the TLA device in allergic asthma, in this pragmatic, placebo-controlled RCT we were unable to demonstrate any effect on exacerbation frequency and only some of the secondary outcomes. Despite the multiple sources of exacerbation data, it is possible that the numbers of exacerbations may have been under-reported although the source of missing data was not the primary source for capturing exacerbations. Any further trial would need to have a singular, robust measure of exacerbations and more detailed assessment of device adherence in this population. Although it was not the primary aim of this Trial, we found that the use of modern techniques of social media can enhance trial recruitment, and they are superior to more traditional methods in this population of severe allergic asthma patients.

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APPENDIX A: LASER PARTICIPANT INFORMATION SHEET (PIS) QUANTITATIVE

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NHS Trust

Respiratory Department, Level C
Queen Alexandra Hospital
Southwick Hill Road
Cosham, Portsmouth
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PATIENT INFORMATION SHEET

laser
A breath of fresh air in asthma

The LASER Trial

Laminar Airflow in Severe Asthma for Exacerbation Reduction

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.

A clinical trial to test whether a new machine that reduces the number of allergy particles inhaled overnight can help to reduce the number of asthma attacks (exacerbations) in patients with severe allergic asthma.

Invitation to take part

We would like to invite you to take part in our research trial. Before you decide, we would like you to understand why the trial is being done and what it would involve for you.

One of the research trial team will go through this information sheet with you and help to answer any questions that you might have. Please talk to others (family, friends or your GP) about the study if you wish.

The Information sheet is in **2 parts**:

Part 1 will tell you the purpose of the study and what will be involved if you choose to take part.

Part 2 will give you more information about how the trial will be conducted.

Please do ask if you have any questions or if anything is not clear.

Part 1

1.1. What is the trial about?

Acute attacks of asthma (asthma exacerbations) are common and cause a great deal of suffering in asthmatic patients. Current treatments for asthma are not completely effective and new and better treatments are needed.

We would like to test whether a new device that reduces the number of allergy particles in the air (which are known to cause asthma) can help reduce these asthma attacks and improve asthma patients' quality of life.

The device is known as a Temperature Controlled Laminar Airflow (TLA) device or Airsonett® device.

'LASER', the name of the trial, is an acronym for 'Laminar Airflow in Severe asthma for Exacerbation Reduction' – we intend to investigate whether laminar airflow treatment in patients with allergic asthma will reduce the frequency of asthma attacks (exacerbations) in these patients.

The TLA device will be installed in the participant's bedroom and will automatically switch on each night. The machine filters the air, removing allergy particles from the patient's breathing zone to allow the lungs to 'rest' overnight.

1.1.1 Will I get the treatment device?

The trial is a randomised, placebo controlled trial. This means that not all patients will receive an active treatment device. Patients will be randomly allocated so that half receive an active device and half receive a device that has been de-activated (a placebo device.) This will allow us to compare results to see whether treatment with the active device is better. The trial is double blinded – this means that neither you nor the trial team will know whether you have an active or inactive device during the trial period.

The trial will involve 12 months of treatment with either an active or placebo device. Once the 12 month trial period has been completed, participants will be offered the use of an active treatment device for a further 4 years, free of charge, if they wish.

If, during the study period, a participant had been allocated a placebo device then this will be replaced with an active treatment device for the 4 year post-trial period.

1.2. Why have I been invited?

You have been invited to take part in this clinical trial because you have severe asthma. You have been identified as a patient who might benefit from this new type of treatment.

The trial is being conducted in a number of hospitals across the UK. We will be inviting a total of 222 patients with severe and difficult to control, allergic asthma to take part in the trial.

1.3. Do I have to take part?

Taking part in the trial is entirely voluntary.

We will describe the trial and go through this information sheet with you. If you do agree to take part then we will ask you to sign a consent form.

If you agree to take part, you will be free to withdraw from the trial at any time without giving a reason.

Withdrawal from the trial will not have any effect on your usual or on-going asthma care.

1.4. What will happen to me if I am interested in taking part?

You will be invited to attend an Information Event led by the research team and our patient representatives to learn more about what taking part in the trial will involve. You will be shown a live demonstration of the treatment device and a presentation prepared by the trial team. You will be able to ask questions about the device and what taking part in the trial will involve.

You will be given a template of the machine to take home with you to ensure that the machine will fit into your bedroom.

Following the Information Event you will be contacted by a member of the trial team to ask if you are interested in taking part in the trial.

The trial will last for 12 months. During this time you will be asked to attend a number of further appointments (a total of 6 visits to your local hospital during the trial period – where possible these will be scheduled to co-incide with your usual asthma clinic outpatient follow-up visits) where you will be asked to complete questionnaires and perform a number of tests which are detailed below.

The table (Table 1) attached to this information sheet outlines what is required at each visit.

The visits are described in more detail below:

Screening Visit 1

If you agree to participate, you will be asked to attend an appointment called the Screening Visit.

We will ask you to sign a consent form for participation in the trial and will give you a copy of this..

During the visit we will check that you are suitable to take part in the trial and ask a number of questions about your asthma and past medical history. We will perform breathing tests, ask you to fill in a short questionnaire, take a blood test and check for allergies with a skin prick test.

At the screening visit we will also give you a peak flow meter and an 'Asthma Control Diary' to record your asthma symptoms and morning peak flow over a 2 week period prior to the second visit (Randomisation Visit 2.)

At the end of the Screening visit, we will arrange an appointment to see you again in 2 weeks for the Randomisation Visit.

If, following the tests, it is found that you are not eligible to take part in the trial then a member of the team will arrange to meet with you to explain the reason for this.

Randomisation Visit 2

At the Randomisation Visit, we will go through the results of the tests from your Screening Visit to check that you are eligible to take part in the trial.

You will be asked to complete a number of questionnaires about your asthma and some further breathing tests. The questionnaires and breathing tests will show us how well your asthma is controlled and give us more information about your asthma before any treatment is started.

You will be given a LASER diary, to use during the trial, to record whether you have used the device, whether you have needed to take time off from work / study and whether you are on oral steroid (Prednisolone) treatment. You will also be given another Asthma Control Diary to record your asthma symptoms for 2 weeks prior to the next trial visit (after 3 months of treatment.)

If the tests confirm that you are eligible to take part in the trial, arrangements will be made for delivery of a treatment device to your home and installation in your bedroom. You will receive a telephone call within 48 hours of your Randomisation Visit to arrange a convenient time for delivery of the device.

There will be further visits arranged during the 12 month treatment period as described below.

1 Month Telephone Review

1 month after the device is installed you will receive a telephone call to ask about any problems with the treatment device and to ask about how much you have been using the device.

3, 6, 9 Month Visits

At 3, 6 and 9 months after device installation, you will be asked to attend appointments at your local hospital.

During each of these visits, you will be asked to complete further questionnaires and breathing tests.

At each of these visits we will review your LASER diary to see how much you have been using the treatment device and whether you have been on steroid treatment or needed any time off work. We will also review the results from your Asthma Control Diary which you will have completed during the 2 weeks before each of these visits.

Following the 6 month visit, arrangements will be made for an engineer to visit your home to service the machine and change the filter.

12 Month Visit

At the end of the 12 month trial period, we will ask you to attend a final appointment. We will again ask you to complete the questionnaires and breathing tests as well as an additional questionnaire about how helpful you have found the treatment.

We will invite you to take part in a voluntary group discussion (focus group) with 5-10 other patients who have been involved in the trial to help find out what you think of the treatment to help guide what might be changed or improved in the future (see separate information sheet and consent form.) These group discussions will be held towards the end of the trial period and are optional.

Exacerbation Visits

If at any time during the trial, (following the screening visit and until completion of your 12 month treatment period,) you experience an asthma attack we will ask you to contact your local trial team so that they can record that you have had an asthma attack and arrange an additional 'Exacerbation Review' visit where you will be seen for an assessment of your asthma symptoms.

Post-Trial Treatment Period

Once the 12 month trial period has been completed, you will be offered the use of an active TLA treatment device, free of charge, for a further 4 years if you wish. If you had previously been allocated an inactivated placebo device then this will be exchanged for an active device at the end of the 12 month trial period.

1.5. Information about the Airsonett® device

The Airsonett® device is a machine designed to be used in your home to reduce your exposure to allergy particles during the night whilst you are asleep.

The treatment is for patients who, despite taking their asthma medications, still have symptoms. The treatment is used in addition to your other asthma treatments. It is non-invasive – not requiring any masks or other uncomfortable equipment and there are no known side effects.

The device will not record any sound or images.

In previous trials, the machine has been shown to be safe for patients and effective in reducing symptoms of asthma. This trial aims to explore whether the treatment can reduce the frequency of asthma attacks as well.

(Figure1) An Airsonett® device being used at a patients' bedside:

Technical Facts - Airsonett®

Weight: 25kg
Height: 94-139cm (depending on type of bed)
Base unit - Length: 54cm Width: 34cm
Energy Consumption: Equivalent to 1 standard 60W light bulb

Further written information about the Airsonett® device can be provided on request.

1.6. Will my expenses be covered?

We will try to arrange your visits for the trial to be at the same time as your routine outpatient visits to the asthma clinic. If however you are required to attend visits in addition to your routine appointments then we are able to reimburse reasonable additional travel expenses.

The cost of electricity required for the use of the Airsonett device for the duration of the trial period will be reimbursed on a pro rata basis at £2/month.

You will be given £25 for attendance at each study visit during the trial period.

1.7. What are the possible benefits of taking part?

We cannot promise that the trial will help you but the information that we gain from the trial will help to guide and improve the treatment of other people with asthma in the future.

1.8. What happens when the research trial stops?

At the end of the research trial you will be offered the use of an active Airsonett® device for a further 4 years, free of charge including engineering support and filter changes. If you had an inactive placebo device during the trial period, this will be exchanged for an active TLAdevice for the 4 year post trial period.

1.9. What if there is a problem?

Any complaint about the way you have been dealt with during the trial or any possible harm you might suffer will be addressed. The detailed information on this is given in Part 2.

1.10. Will my taking part in the trial be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence.

This completes **Part 1**

If the information in **Part 1** has interested you and you are considering participation, please read the additional information in **Part 2** before making any decision.

Part 2

2.1. What if relevant new information becomes available?

The trial team will continue to review all new research data. If new information that influences the trial becomes available, alterations will be made accordingly. If this changes your involvement in the trial then you will be contacted with an updated information sheet and asked to sign a further consent form.

Your right to withdraw from the trial remains the same with there being no impact on your normal asthma care.

2.2. What if I don't want to continue in the study?

If you decide that you do not want to continue with the study then your research doctor will make arrangements for your usual asthma care to continue. You do not have to give a reason for your withdrawal from the study.

If you withdraw from the study, we will destroy any identifiable blood samples or data if you wish.

We may still need to use the data collected up until the point of your withdrawal in the analysis of the trial results.

Early withdrawal from the study may impact on your eligibility for the 4 year post trial treatment period with the active Airsonett® treatment device.

2.3. What if there is a problem?

If you have a concern about any aspect of this study or your wider care then we would encourage you to ask to speak to a trial doctor or nurse who will do their best to resolve any issues you may have.

If you remain unhappy and wish to make a formal complaint then you can do this through the NHS complaints procedure. We can provide you with information on how to contact either the Patient Advice and Liaison Service (PALS) or the hospital complaints manager. These details can also be obtained through the hospital switchboard.

If you are harmed as a result of your participation in this study, due to someone's negligence, Portsmouth Hospitals NHS Trust will provide indemnity and / or compensation via the NHS indemnity scheme.

2.4 Will my taking part in the study be kept confidential?

All information which is collected about you during the course of the study will be kept strictly confidential.

2.5 Will my General Practitioner (GP) be informed?

You are asked on the consent form to give permission for us to let your GP know that you are taking part in the study.

We may also need to contact your GP for more information about you. If so, you will be told and you will be given a copy of any correspondence with your GP.

2.6 What will happen to the results of the trial?

When the trial has finished the results will be analysed. The results of the trial will then be published in a medical journal so that other doctors can read them and learn from them. No individual patients will be identifiable from the results published.

If you would like a copy of the medical paper, or would like us to write to you personally to explain the study findings then please indicate this on your consent form.

2.7 Who is organising and funding the research

Portsmouth Hospitals NHS Trust is sponsoring the research trial. This means that the trust has overall responsibility for the trial ensuring that it is conducted in a safe and appropriate manner.

The study has been funded by a research grant from the National Institute for Health Research.

None of the investigators performing the research will benefit financially from the study.

2.8 Who has reviewed and approved the trial?

All research in the NHS is looked at by an independent group of people called the Research Ethics Committee in order to protect your interests.

This study has been reviewed and approved by XXX ethics committee, as well as by the doctors and research department in your own hospital.

2.9 What do I need to do now?

After reading this information sheet you will be invited to ask questions about the trial. If you would like to take part then we shall ask you to sign a consent form, which will also ask if you want your GP to be informed of your involvement. If you would like some extra time to consider entry into the trial, to discuss with your friends, family or your GP, then please let us know.

If you decide not to participate, your routine medical care and your legal rights will not be affected in any way.

If you agree to participate in the trial you are free to withdraw at any time without giving a reason.

Contact details:

Your local principal investigator is:	Dr.XXX Tel: XXXXX XXXXXX Ext:XXX
For routine trial-related questions during working hours, please contact:	(Research Nurses) Tel: XXXXX XXXXXX Ext: XXXX
For further information about research and clinical trials in your local area, please contact:	Research and Development Office XXXXX XXXXXX Ext: XXXX
To speak to your local hospital's Advice and Complaints Team, please contact:	The Patient Advice and Liaison Service Telephone: XXXXX XXXXXX

For emergency or non-trial-related medical issues please contact medical services as normal.

APPENDIX B: LASER PARTICIPANT INFORMATION SHEET (PIS) QUALITATIVE

Portsmouth Hospitals NHS
NHS Trust

Respiratory Department, Level C
Queen Alexandra Hospital
Southwick Hill Road
Cosham, Portsmouth
Hampshire, PO6 3LY
Tel: 02392 286000 Ext 4108

PATIENT INFORMATION SHEET

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Qualitative Assessment

(Participant - *Main Study*)

A Qualitative Study to Explore the Use of Temperature Controlled Laminar Airflow (TLA) in the Treatment of Severe Asthma

Please take some time to read through this information sheet and if you wish discuss with your family, friends or GP.
Please ask if anything is not clear or if you would like any further information regarding the study.

1.1. What is the background of this study?

The Laser Trial is a study investigating the use of a new treatment in asthma, Temperature-controlled Laminar Airflow (TLA). The treatment is home based and we are interested to hear your experiences and views of the treatment in order to determine whether it is a viable treatment option that might be adopted across the NHS if shown to be of benefit in patients with asthma.

This part of the LASER trial is a qualitative study where we will explore participant's experiences of the TLA treatment device. Participants will be asked to take part in a focus group with other participants who have taken part in the trial.

What is a focus group?

A Focus Group is a group discussion bringing together a group of people to take part in a carefully planned discussion to discuss their views on a defined area of interest. The group will generally be small (no more than 10 participants) and will be led by an experienced facilitator.

1.2. Why have I been invited?

We are asking all participants who are enrolled in the LASER trial to take part in the qualitative study.

We will hold 4 focus groups at different locations in order to get a representative sample of the trial participants. We will ask you to take part in ONE focus group only.

If you do agree to take part in the qualitative study, we do not guarantee that we will select you to take part in the focus group. This is because we need to have a representative sample of participants that is balanced for age, gender and location.

If you agree to take part but are not selected for the qualitative interview then a member of the trial team will contact you to inform you of this.

1.3. Do I have to take part?

Taking part in the qualitative study is entirely optional. If you do not wish to be included in this part of the trial then your participation in the rest of the LASER Trial will not be compromised.

If you do agree to take part in the qualitative study then we will ask you to sign a separate consent form.

If you agree to take part in the qualitative study, you will be free to withdraw at any time without compromising your ongoing participation in the LASER Trial. You will not be expected to give a reason for withdrawing from the qualitative study.

1.4. What will happen to me if I do decide to take part?

If you are selected to take part in the qualitative interview we will arrange a mutually acceptable time to telephone you during the last 2 months of the trial to arrange for you to take part in a focus group discussion about the treatment and your experience of using the device.

The focus group will consist of 5-10 other LASER trial participants and 2-3 facilitators who will be making notes and recording the discussions.

During the focus group interview, an experienced interviewer will ask the group's opinions, views and questions about the trial and the TLA treatment device.

What will be expected from me?

During the focus group, we would like you to contribute YOUR views as part of the discussion. There are no right or wrong answers and we are keen to hear a range of views. Topics to be considered at the focus group session are likely to include:

- Were there any problems with installing the TLA device in your home?
- Was the TLA device easy to use?
- Were you given adequate instructions for using the TLA device
- Did you experience any technical difficulties with the TLA device?
- Was there adequate technical support if required?
- What problems did you find with the TLA device?
- How might we improve the TLA device?
- Would you be happy to continue with the TLA treatment outside of the LASER trial?

1.5. How long will the interview last?

The focus group interview is likely to last for at least 1 hour. The interview may take longer than this if participants wish but will not take longer than 2 hours.

1.6. Will the interview be audi-taped / recorded?

Yes, the interview will be audio-taped.

The audio-tapes will be kept safely and confidentially at the University of Portsmouth. The tapes will be transcribed verbatim by the moderator without referring to the name of the participants.

What you disclose in the interview will not be shared with other people. Transcribed quotes from the interview will have no information that would reveal your identity.

1.7. What will I get from participating in the interview?

All participants who take part in the qualitative focus group will receive a £10 gift voucher for their time.

1.8. Who should I contact if I require further information?

Should you require any further information or wish to discuss the qualitative interview further then please do not hesitate to ask / contact us.

Your local principal investigator is:	Dr. Tel: XXXXX XXXXXX Ext:XXXX
For questions related to this study, please contact:	(Research Nurses) Tel: XXXXX XXXXXX Ext: XXXX

APPENDIX C: LASER CONSENT FORM QUANTITATIVE

Centre Number:..... Participant Initials..... Participant ID Number: .....

Portsmouth Hospitals NHS
NHS Trust

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CONSENT FORM

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.

Chief Investigator: **Professor Anoop J. Chauhan**

Please initial all boxes

1. I confirm that I have read and understand the information sheet dated **[DATE]** (version **[VERSION NUMBER]**) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from the research trial team, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐
4. I agree to my contact details (Telephone Number and Address) being passed on to Oxford Clinical Trials Research Unit and the Engineering Team to allow arrangements to be made for allocation and delivery of the trial treatment device. ☐
5. I agree to blood samples being taken for the purposes of this study. ☐
6. I agree to my GP being informed of my participation in the study. ☐
7. I agree to take part in the above study. ☐

Name of Participant	Date	Signature
Name of Person taking Consent	Date	Signature

Consent form date of issue: **[DATE]**
Consent form version number: **[VERSION]**

Page 1 of 1

APPENDIX D: LASER CONSENT FORM QUALITATIVE

Centre Number:..... Participant Initials..... Participant ID Number: .....

Portsmouth Hospitals NHS
NHS Trust

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CONSENT FORM

A Qualitative Study to Explore the Use of Temperature Controlled Laminar Airflow in the Treatment of Severe Asthma.

Chief Investigator: **Professor Anoop J. Chauhan**

Please initial all boxes

1. I confirm that I have read and understand the information sheet dated **[DATE]** (version **[VERSION NUMBER]**) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that withdrawal from the qualitative study will not compromise my further participation in The LASER Trial. ☐
4. I am willing to consent to the use of audio-taping of the interview and for this audio-recording to be transcribed for use as verbatim quotation. I understand that any information that I give will only be used anonymously and I will not be identified when my views are used in any publications or reports. ☐
5. I agree to the use of audio-clips of the recording for presentation purposes when disseminating the results of the study. ☐
6. I agree to being contacted by telephone to arrange a mutually convenient time for the qualitative interview. ☐
7. I agree to my GP being informed of my participation in the study. ☐
8. I agree to take part in the above study. ☐

Name of Participant	Date	Signature
Name of Person taking Consent	Date	Signature

Consent form date of issue: **[DATE]**
Consent form version number: **[VERSION]**

Page 1 of 1

APPENDIX E: FAVOURABLE ETHICS OPINION LETTER

NHS
Health Research Authority

NRES Committee South Central - Berkshire
Bristol REC Centre
Whitefriars
Level 3, Block B
Lewins Mead
Bristol
BS1 2NT

Telephone: 0117 342 1333
Facsimile: 0117 342 0445

26 February 2014

Prof Anoop Chauhan
Consultant Respiratory Physician and Director of Research and Development
Portsmouth Hospitals NHS Trust
Department of Respiratory Medicine
Queen Alexandra Hospital
Southwick Hill Road, Cosham, Portsmouth
PO6 3LY

Dear Prof Chauhan

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 asthsma.**
REC reference:	**14/SC/0092**
IRAS project ID:	**148386**

The Research Ethics Committee reviewed the above application at the meeting held on 18 February 2014. Thank you for attending, along with Dr Storrar, to discuss the application.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the REC Manager Ms Rae Granville, nrescommittee.southcentral-berkshire@nhs.net.

Ethical Considerations

1. The Committee noted that the partners and carers of participants are requested to complete a questionnaire and are part of the pilot phase and receive information sheets and consent/declaration forms, but their involvement is not detailed in the REC Form.

2. The Committee commented on the device. It requested further details on the device's history. You explained that the device was manufactured in Sweden. You explained how the device functioned and added that it reduced allergens by 99%. The Committee questioned if more allergens might be created by the removal of the filter in the placebo

devices. You explained that the filter was bypassed by a micro puncture thus the laminar flow was disabled. The Committee queried whether the laminar flow could create turbulence around the participant's head. You answered that this device had been trial tested in the 4A project, which looked at particle counts with patients suffering different levels of asthma. It concluded that the particle count was negligible and would not deliver more allergens to participants. The Committee was content with this reply.

3. The Committee observed that there was no reference to the noise level of this device in the information sheet. You replied that the device made little noise, similar to air conditioning. In the 4A project only 1-2 participants dropped out due to the noise level. The Committee requested that this description be included in the information sheet. You agreed.

4. The Committee queried if the opening of the bedroom window would cause a problem with the device's function. You replied that only extreme wind force would cause an issue. You added that you have asked the company who had indicated that the device could be used as part of a normal life style. Opening windows would not be an issue.

5. The Committee queried what happened to the machine after the four years of trial provision. It questioned why you did not give the machine to the participant if it proved effective. The Committee suggested that a policy be put in place to confirm that the participant could keep the device for as long as it worked. You agreed. You explained that the device cost £175. If the trial is a success and shows that the device is beneficial you could make a case with NICE. They have four years to resolve this.

Ethical opinion

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Ethical review of research sites

NHS Sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

1. As agreed in point three, please add an indicator of the noise level to the information sheet.

2. The Committee notes the researchers' assurance that participants will be able to retain the device at the end of the four years and that if the device proves to be successful funding through NICE will be sought.

APPENDIX F: LASER TRIAL VISIT SCHEDULE

Table F1: LASER visit schedule up to 12 months, including time points for CRFs, FUs, Questionnaires and Diaries

	Data Collection Time Point							
	Screening	**Randomisation**	**1 Month**	**3, 6, 9, 12 Months**	**Exacerbation**	**ADE**	**SADE**	**Withdrawal**
CRFs / FUs								
Screening Visit	X							
Randomisation Visit		X						
Randomisation Form		X						
1 Month Telephone Follow-up			X					
3 Month Visit				X				
Exacerbation Review					X			
ADE Form						X		
SADE Form							X	
Withdrawal Form								X
Questionnaires (Participant)								
ACQ	X	X		X				
AQLQ(S)		X		X				
EQ-5D-5L		X		X				
SNOT-22		X		X				
WPAI (A)		X		X				
Indoor Air Quality		X						
Questionnaires (Carer)								
AC-QoL		X						
WPAI (CG)		X						
Diaries								
Asthma Control - Screening		X						
Asthma Control - Follow-up				X				
TLA - Laser Diary				X				
Healthcare Resource Use diary				X				
Exacerbation Diary					X			

APPENDIX G: COMPARATIVE TRIALS SHOWING EFFICACY FOR SAMPLE SIZE AND MAGNITUDE OF EFFECT

Table G1: 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 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 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 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 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 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 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 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 1997	Symbicort	852	Not recorded	**0.91**	0.34 vs 0.91	**63%**	Low to Moderate	Requiring OCS

APPENDIX H: EQUIVALENCE TABLE FOR BRONCHIAL CHALLENGE TESTING

Table H1: Equivalence table for bronchial challenge testing

Challenge Test	Positive Result
Direct	
Methacholine	PC_{20} <8mg/ml
Histamine	PC_{20} <8mg/ml
Indirect	
Mannitol	PD_{15} <635mg[i]
Exercise	Fall in FEV_1 of ≥10% from baseline[ii]

i Positive Result is > 15% FEV_1 drop from baseline OR > 10% FEV_1 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 conformed to international quality guidance (Crapo et al 2000) (Anderson et al 1997)

APPENDIX I: DEFINITION OF HIGH DOSE INHALED CORTICOSTEROIDS

Table I1: Definition of High Daily Dose of Inhaled Corticosteroids

(Table modified from the International ERS/ATS Guidelines on Definition, Evaluation and Treatment of Severe Asthma 2013)

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 J: INTERFERENCE OF MEDICATIONS WITH SPT REACTIONS

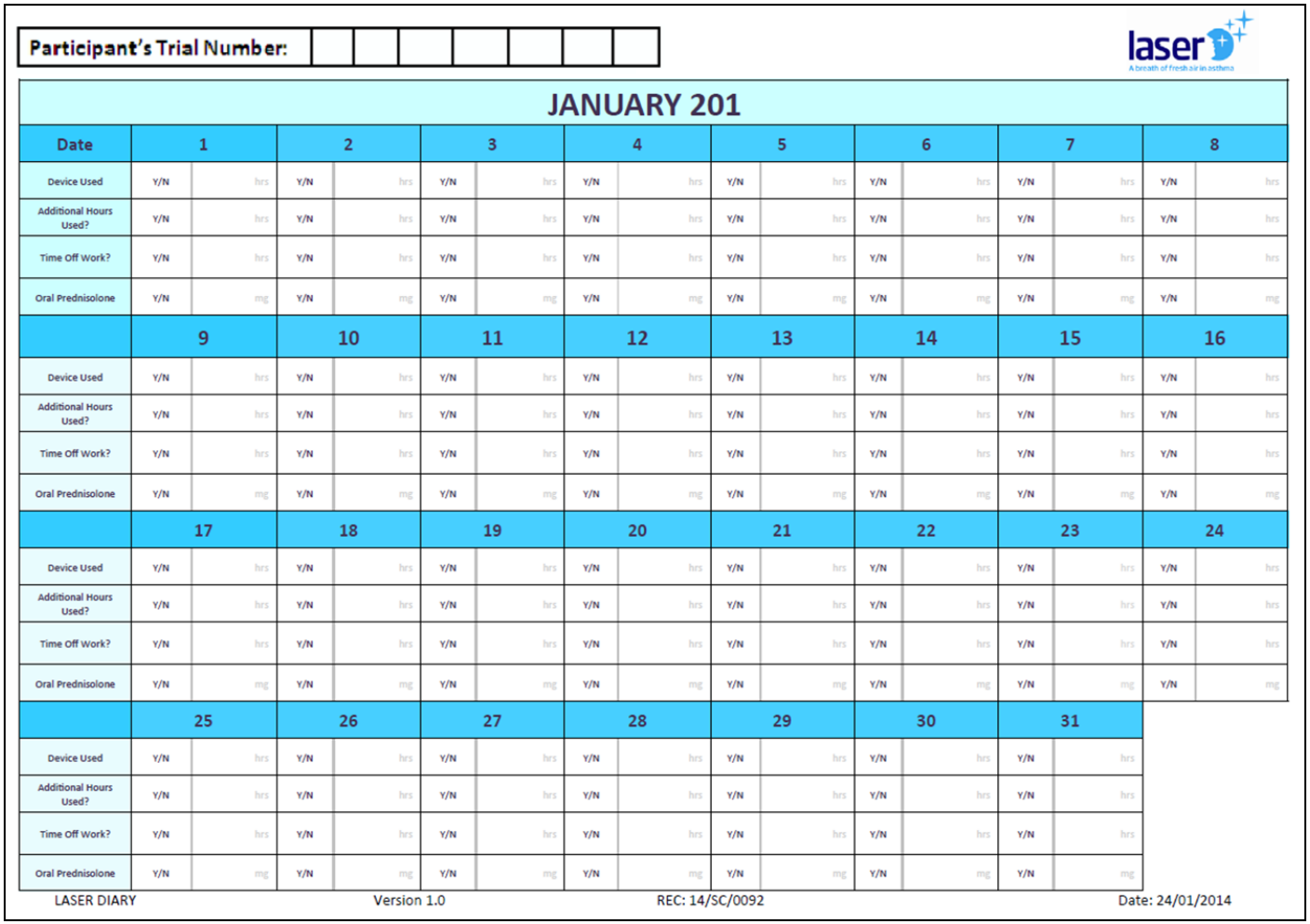
Table J1: Potential interference of medications with skin prick test reactions. Adapted from Castro et al (2009)

Drug	Abstinence Required Before Testing
Antihistamines	
1st Generation H1-anti-histamines *Hydroxyzine*	 >2 days
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 who were taking maintenance oral corticosteroids and who had a negative skin-prick test and supportive history of atopy proceeded to specific IgE testing.

If there was any doubt as to the result of the skin prick tests when assessing eligibility criteria, allergic status was then confirmed with specific IgE testing (see Section 2.10.1.3.)

APPENDIX K: TLA DIARY



Participant's Trial Number: | | | | | | | |

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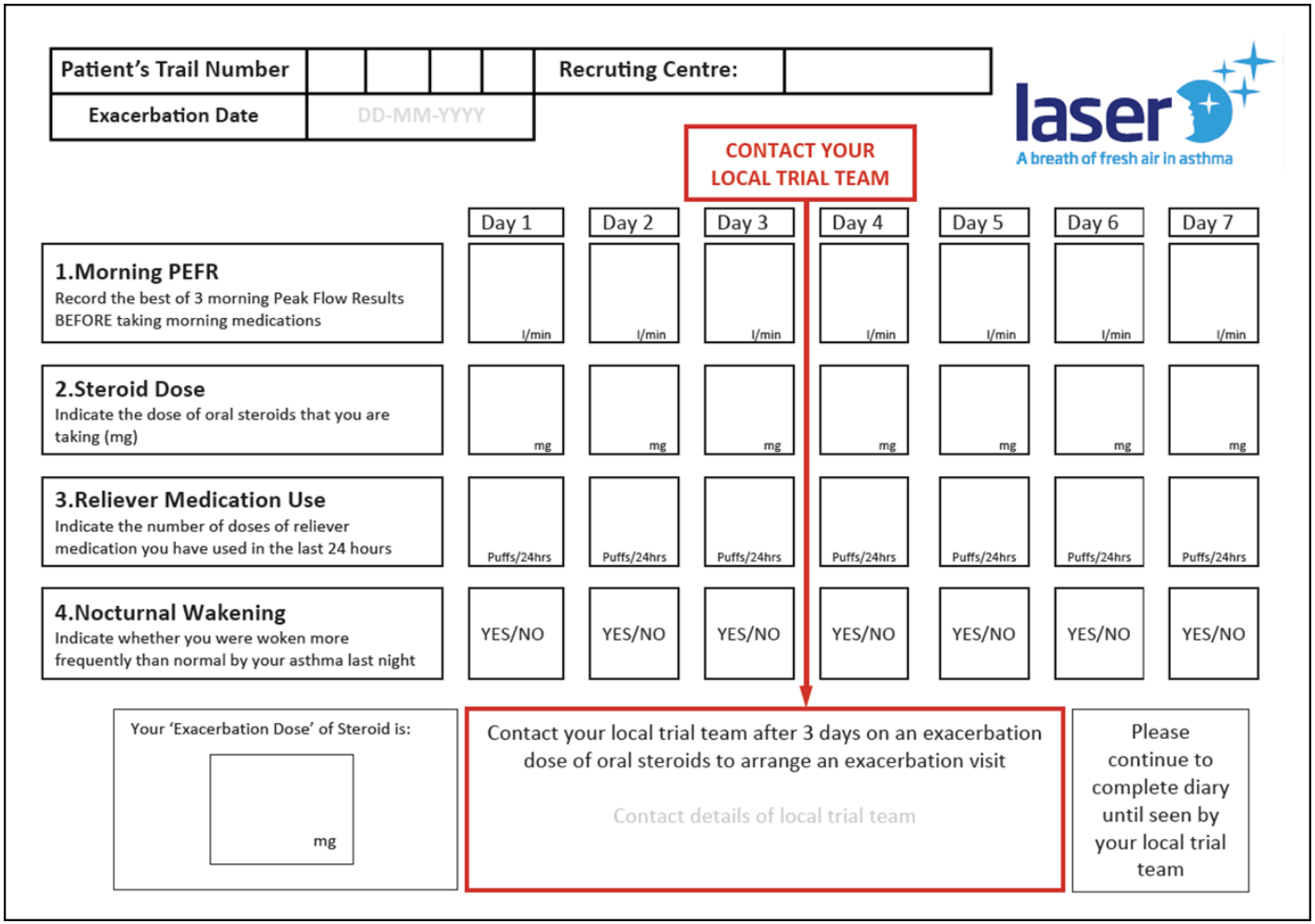
JANUARY 201

Date	1		2		3		4		5		6		7		8	
Device Used	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs
Additional Hours Used?	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs
Time Off Work?	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs
Oral Prednisolone	Y/N	mg	Y/N	mg	Y/N	mg	Y/N	mg	Y/N	mg	Y/N	mg	Y/N	mg	Y/N	mg
	9		10		11		12		13		14		15		16	
Device Used	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs
Additional Hours Used?	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs
Time Off Work?	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs
Oral Prednisolone	Y/N	mg	Y/N	mg	Y/N	mg	Y/N	mg	Y/N	mg	Y/N	mg	Y/N	mg	Y/N	mg
	17		18		19		20		21		22		23		24	
Device Used	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs
Additional Hours Used?	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs
Time Off Work?	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs
Oral Prednisolone	Y/N	mg	Y/N	mg	Y/N	mg	Y/N	mg	Y/N	mg	Y/N	mg	Y/N	mg	Y/N	mg
	25		26		27		28		29		30		31			
Device Used	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs		
Additional Hours Used?	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs		
Time Off Work?	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs	Y/N	hrs		
Oral Prednisolone	Y/N	mg	Y/N	mg	Y/N	mg	Y/N	mg	Y/N	mg	Y/N	mg	Y/N	mg		

LASER DIARY Version 1.0 REC: 14/SC/0092 Date: 24/01/2014

APPENDIX L: PARTICIPANT EXACERBATION DIARY (PED)



Patient's Trail Number					Recruting Centre:	
Exacerbation Date	DD-MM-YYYY					

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CONTACT YOUR LOCAL TRIAL TEAM

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
1.Morning PEFR Record the best of 3 morning Peak Flow Results BEFORE taking morning medications	l/min	l/min	l/min	l/min	l/min	l/min	l/min
2.Steroid Dose Indicate the dose of oral steroids that you are taking (mg)	mg	mg	mg	mg	mg	mg	mg
3.Reliever Medication Use Indicate the number of doses of reliever medication you have used in the last 24 hours	Puffs/24hrs	Puffs/24hrs	Puffs/24hrs	Puffs/24hrs	Puffs/24hrs	Puffs/24hrs	Puffs/24hrs
4.Nocturnal Wakening Indicate whether you were woken more frequently than normal by your asthma last night	YES/NO	YES/NO	YES/NO	YES/NO	YES/NO	YES/NO	YES/NO

Your 'Exacerbation Dose' of Steroid is:

mg

Contact your local trial team after 3 days on an exacerbation dose of oral steroids to arrange an exacerbation visit

Contact details of local trial team

Please continue to complete diary until seen by your local trial team

APPENDIX M: EXACERBATION REVIEW FORM (REV)

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Form 9 – Exacerbation Review

Participant's trial number: L A S | **Date of Review:** DD / MM / YYYY | **Participant's initials:**

SECTION 1 – EXACERBATION REVIEW

1.	NATURE OF REVIEW? (Please tick ONE)	FACE TO FACE REVIEW	TELEPHONE REVIEW
2.	DATE OF ONSET OF SYMPTOMS?	DD / MM / YYYY	
3.	CURRENT DOSE OF PREDNISOLONE ____ mg	3a. DATE COMMENCED	DD / MM / YYYY
4.	ANY OTHER TREATMENT CHANGES? (Please tick ONE)	YES	NO
	Specify: _____		

SECTION 2 – REVIEW OF EXACERBATION DIARY

(Please refer to protocol for the definition of a Severe Asthma Exacerbation (Section 11.6.1.1))

CORROBORATION OF DIAGNOSIS OF SEVERE EXACERBATION

1.	≥ 30 MG PREDNISOLONE DAILY (OR ≥ 50% INCREASE IN DOSE IF MAINTENANCE 30 MG PREDNISOLONE OR ABOVE)? (Please tick ONE)	YES	NO
2.	≥ 3 DAYS DURATION? (Please tick ONE)	YES	NO

WORSENING OF ASTHMA SYMPTOMS CORROBORATED BY AT LEAST ONE OF THE FOLLOWING:

1.	A DECREASE IN MORNING PEF COMPARED TO MAXIMUM MORNING PEF ACHIEVED AT BASELINE? (Please tick ONE)	YES	NO
2.	A 50% INCREASE IN RELIEVER MEDICATION ON AT LEAST 2 OF 3 SUCCESSIVE DAYS COMPARED TO BASELINE? (Please tick ONE)	YES	NO
3.	AN INCREASE IN NOCTURNAL WAKENING BY ASTHMA SYMPTOMS COMPARED TO NORMAL? (Please tick ONE)	YES	NO
4.	EXACERBATION CONFIRMED? (Please tick ONE)	YES	NO

4a IF YES, DATE: DD/MM/YYYY | 4b. BY WHO

CHECKLIST (Tick if when done, if applicable)

Exacerbation Diary Card sent to ORTU	YES	NO
Participant asked to continue to record daily prednisolone dose on LASER diary	YES	NO
Participant issued with replacement Exacerbation Diary Card	YES	NO

		DD	MM	YYYY
Name of researcher completing form	Signature	Date		

LASER TRIAL Form 9 – Exacerbation Review CRF Version: 1.0 Date: 06MAY2014 Page 1 of 1

APPENDIX N: LASER FOCUS GROUP INTERVIEW SCHEDULE

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Focus Group Interview Schedule

A Qualitative Study to Explore the Use of Temperature Controlled Laminar Airflow (TLA) in the Treatment of Severe Asthma and Participant's Experience of Taking Part in the LASER Trial

Participant Identification Number	_____
Date of Interview	_____
Time of Interview	_____
Qualitative Patient Information Sheet (Version_____Date_____)	**YES** □ **NO**□
Consent Form Signed (Version_____Date_____)	**YES** □ **NO**□
Test Recording Equipment	**YES** □ **NO**□
Verbal Confirmation of Participant Consent	**YES** □ **NO**□
Verbal Explanation of Qualitative Study before starting interview	**YES** □ **NO**□

This is a brief overview of the topics to be considered. It is likely that the content of the interview schedule will develop and may incorporate other areas as the researcher reflects on responses during the focus group.

The 'Prompts/Explore' sections in *italics* will only be raised if not covered spontaneously by participants.

TOPIC AREA 1 – Device Delivery and Installation

Were there any problems with installing the device?

Prompts / Explore
- *Was the device delivered at a convenient time?*
- *Were the engineering team helpful?*
- *Was any bedroom modification necessary to accommodate the device?*
- *Did you receive adequate instructions on using the device?*

TOPIC AREA 2 – Device Use

What has been your experience of using the device?

Prompts / Explore
- *Is there anything stopping you from using the device?*
- *Have you encountered any technical problems?*
- *Do you have any positive experiences to report?*
- *Do you have any negative experiences to report?*

TOPIC AREA 3 – Design Features

Do you have any suggestions on how the device might be improved or modified for future users?

TOPIC AREA 4 – Any other comments?

Is there anything else that you would like to say or comment on?

Thank Participants for taking part in the Qualitative Interview
Assure participants of confidentiality of responses
Switch off recording device

APPENDIX O: QUALITY OF LIFE EQ-5D-5L RESPONSES

Table L1: Quality of Life EQ-5D-5L Responses

	Randomisation	3 months	6 months	9 months	12 months
Placebo, n (%)					
Mobility					
No problems in walking about	38 (32)	46 (44)	44 (44)	33 (35)	37 (39)
Slight problems in walking about	28 (23)	14 (13)	17 (17)	17 (18)	22 (23)
Moderate problems in walking about	33 (28)	29 (28)	26 (26)	35 (37)	24 (25)
Severe problems in walking about	21 (18)	16 (15)	13 (13)	10 (11)	13 (14)
Unable to walk about	0	0	1 (1)	0	0
Self-care					
No problems washing or dressing	87 (73)	83 (79)	72 (72)	65 (68)	61 (64)
Slight problems washing or dressing	13 (11)	11 (10)	17 (17)	13 (14)	22 (23)
Moderate problems washing or dressing	17 (14)	9 (9)	8 (8)	10 (11)	9 (9)
Severe problems washing or dressing	2 (2)	2 (2)	3 (3)	5 (5)	4 (4)
Unable to wash or dress	0	0	1 (1)	2 (2)	0
Usual activities					
No problems doing usual activities	24 (20)	32 (31)	34 (34)	30 (32)	31 (32)
Slight problems doing usual activities	38 (32)	23 (22)	20 (20)	20 (21)	28 (29)
Moderate problems doing usual activities	40 (34)	33 (32)	34 (34)	28 (29)	25 (26)
Severe problems doing usual activities	17 (14)	13 (13)	10 (10)	15 (16)	10 (10)
Unable to do usual activities	0	3 (3)	3 (3)	2 (2)	2 (2)
Pain / discomfort					
No pain or discomfort	45 (38)	40 (38)	37 (37)	35 (37)	37 (39)
Slight pain or discomfort	33 (28)	29 (28)	29 (29)	20 (21)	25 (26)
Moderate pain or discomfort	28 (23)	24 (23)	24 (24)	26 (27)	19 (20)
Severe pain or discomfort	12 (10)	9 (9)	9 (9)	12 (13)	12 (13)
Extreme pain or discomfort	2 (2)	3 (3)	2 (2)	2 (2)	3 (13)
Anxiety / depression					
Not anxious or depressed	61 (51)	57 (54)	54 (53)	45 (47)	54 (56)
Slightly anxious or depressed	29 (24)	26 (25)	24 (24)	24 (25)	15 (16)
Moderately anxious or depressed	21 (18)	12 (11)	8 (8)	14 (15)	15 (16)
Severely anxious or depressed	6 (5)	7 (7)	14 (14)	9 (9)	10 (10)
Extremely anxious or depressed	3 (3)	3 (3)	1 (1)	3 (3)	2 (2)
TLA device, n (%)					
Mobility					
No problems in walking about	49 (43)	49 (49)	43 (44)	43 (48)	45 (50)
Slight problems in walking about	24 (21)	21 (21)	23 (24)	16 (18)	20 (22)
Moderate problems in walking about	31 (27)	22 (22)	20 (21)	23 (26)	16 (18)
Severe problems in walking about	11 (10)	7 (7)	10 (10)	8 (9)	9 (10)
Unable to walk about	0	0	0	0	0
Self-care					
No problems washing or dressing	86 (75)	78 (80)	74 (77)	73 (81)	71 (79)
Slight problems washing or dressing	14 (12)	11 (11)	13 (14)	8 (9)	11 (12)
Moderate problems washing or dressing	13 (11)	6 (6)	9 (9)	7 (8)	5 (6)
Severe problems washing or dressing	2 (2)	3 (3)	0	2 (2)	3 (3)
Unable to wash or dress	0	0	0	0	0
Usual activities					
No problems doing usual activities	34 (30)	37 (37)	38 (40)	38 (42)	46 (51)
Slight problems doing usual activities	39 (34)	31 (31)	27 (28)	24 (27)	18 (20)

Moderate problems doing usual activities	29 (25)	21 (21)	20 (21)	17 (19)	19 (21)
Severe problems doing usual activities	11 (10)	10 (10)	9 (9)	10 (11)	7 (8)
Unable to do usual activities	2 (2)	0	2 (2)	1 (1)	0
Pain / discomfort					
No pain or discomfort	42 (37)	37 (38)	36 (37)	34 (38)	35 (39)
Slight pain or discomfort	33 (29)	31 (32)	31 (32)	30 (33)	26 (29)
Moderate pain or discomfort	22 (19)	24 (24)	22 (23)	15 (16)	23 (26)
Severe pain or discomfort	15 (13)	5 (5)	4 (4)	10 (11)	4 (4)
Extreme pain or discomfort	3 (3)	1 (1)	3 (3)	1 (1)	2 (2)
Anxiety / depression					
Not anxious or depressed	64 (56)	59 (60)	55 (57)	52 (58)	57 (63)
Slightly anxious or depressed	26 (23)	22 (22)	26 (27)	25 (28)	16 (18)
Moderately anxious or depressed	17 (15)	12 (12)	10 (10)	11 (12)	12 (13)
Severely anxious or depressed	7 (6)	3 (3)	4 (4)	2 (2)	4 (4)
Extremely anxious or depressed	1 (1)	2 (2)	1 (1)	0	1 (1)

APPENDIX P: PARTICIPANTS WITHDRAWAL DATA

Table M1: Full details of participants with withdrawal reports, deaths and those not meeting minimum data requirements

Description of withdrawal	Withdrawal Reason	Reason for Withdrawal Reason specified	Withdrew consent to use prior data	Had minimum data	Death	Follow-up Visits received	Participant group
Did not meet minimum data requirement				No		3 6 9 12	Placebo
Did not meet minimum data requirement				No		3 6 9 12	Active
Did not meet minimum data requirement				No		3 6 9 12	Placebo
Did not meet minimum data requirement				No		3 6 9 12	Placebo
Did not meet minimum data requirement				No		~X~ 6 9 12	Placebo
Did not meet minimum data requirement				No		~X~ 6 9 12	Placebo
Did not meet minimum data requirement				No		3 6 9 12	Active
Death				Yes	Yes	3 6 9 ~X~	Placebo
Data Withdrawal			Yes	No		~X~~X~~X~~X~	Active
Data Withdrawal			Yes	No		~X~~X~~X~~X~	Placebo
Data Withdrawal			Yes	No		~X~~X~~X~~X~	Active
Data Withdrawal			Yes	No		~X~~X~~X~~X~	Active
Data Withdrawal			Yes	No		~X~~X~~X~~X~	Active
Withdrawal Form completed	Ineligibility			Yes		3 6 ~X~~X~	Placebo
Withdrawal Form completed	Ineligibility			Yes		3 6 ~X~~X~	Active
Withdrawal Form completed,	Other	"Death, patient"		No	Yes	~X~~X~~X~~X~	Active

Death							
Withdrawal Form completed	Other	Constant sneezing when using TLA device		No		~X~~X~~X~~X~	Placebo
Withdrawal Form completed	Other	Getting headaches and sore throats from the device.		Yes		3 ~X~~X~~X~	Placebo
Withdrawal Form completed	Other	Increased asthma severe exacerbations		No		3 ~X~~X~~X~	Placebo
Withdrawal Form completed	Other	Machine didn't fit in room		No		~X~~X~~X~~X~	Active
Withdrawal Form completed	Other	Mental health problems		Yes		3 6 ~X~~X~	Active
Withdrawal Form completed	Other	Moving house again		Yes		3 6 ~X~~X~	Placebo
Withdrawal Form completed	Other	Non compliance of device. Did not attend study visits.		Yes		~X~~X~~X~~X~	Active
Withdrawal Form completed	Other	Not wanting to participate any more.		Yes		3 ~X~~X~~X~	Placebo
Withdrawal Form completed	Other	Participant DNA'd multiple visits and is not responding to telephone calls		No		~X~~X~~X~~X~	Placebo
Withdrawal Form completed	Other	Participant has left the family home and is unable to use the machine or have it re-installed elsewhere and wishes to withdraw from the study		No		~X~ 6 ~X~~X~	Active
Withdrawal Form completed	Other	Participant moved out of area and did not with to continue FU at another hospital		Yes		3 ~X~~X~~X~	Active
Withdrawal Form completed	Other	Participant became unwell following a PG and pressures of new pregnancy - contributed to decision to withdraw		No		~X~~X~~X~~X~	Placebo
Withdrawal Form completed	Other	Participant did not attend appointments or respond to phone contact		No		3 ~X~~X~~X~	Placebo

Withdrawal Form completed	Other	Participant unable to commit to last appointment		No		3 6 9 ~X~	Placebo
Withdrawal Form completed	Other	Unable to arrange installation of the TLA device.		No		~X~~X~~X~~X~	Placebo
Withdrawal Form completed	Other	Unable to comply with protocol		No		3 ~X~~X~~X~	Active
Withdrawal Form completed	Other	Unable to contact participant		No		~X~~X~~X~~X~	Active
Withdrawal Form completed	Other	Unable to contact participant		No		3 ~X~~X~~X~	Active
Withdrawal Form completed	Other	Unable to contact participant		No		3 ~X~~X~~X~	Placebo
Withdrawal Form completed	Other	Unable to make contact with participant		Yes		3 6 ~X~~X~	Active
Withdrawal Form completed	Other	Participant has moved abroad		No		3 ~X~~X~~X~	Placebo
Withdrawal Form completed	Participant withdrew consent			No		~X~~X~~X~~X~	Active
Withdrawal Form completed	Participant withdrew consent			No		~X~~X~~X~~X~	Active
Withdrawal Form completed	Participant withdrew consent			No		3 ~X~~X~~X~	Placebo
Withdrawal Form completed	Participant withdrew consent			No		~X~~X~~X~~X~	Placebo
Withdrawal Form completed	Participant withdrew consent			No		~X~~X~~X~~X~	Active
Withdrawal Form completed	Participant withdrew consent			No		~X~~X~~X~~X~	Active
Withdrawal Form completed	Participant withdrew consent			No		3 ~X~~X~~X~	Placebo
Withdrawal Form completed	Participant withdrew consent			No		~X~~X~~X~~X~	Placebo
Withdrawal Form completed	Participant withdrew consent			No		~X~~X~~X~~X~	Active
Withdrawal Form completed	Participant withdrew consent			No		3 ~X~~X~~X~	Active
Withdrawal Form completed	Participant			No		3 6 ~X~~X~	Active

	withdrew consent						
Withdrawal Form completed	Participant withdrew consent			No		~X~~X~~X~~X~	Active
Withdrawal Form completed	Participant withdrew consent			No		~X~~X~~X~~X~	Active
Withdrawal Form completed	Participant withdrew consent			No		~X~~X~~X~~X~	Placebo
Withdrawal Form completed	Participant withdrew consent			No		~X~~X~~X~~X~	Active
Withdrawal Form completed	Participant withdrew consent			No		~X~~X~~X~~X~	Placebo
Withdrawal Form completed	Participant withdrew consent			No		3 6 ~X~~X~	Placebo
Withdrawal Form completed	Participant withdrew consent			No		~X~~X~~X~~X~	Placebo
Withdrawal Form completed	Participant withdrew consent			Yes		3 6 9 ~X~	Active
Withdrawal Form completed	Participant withdrew consent			Yes		3 6 ~X~~X~	Active
Withdrawal Form completed	Participant withdrew consent			Yes		3 6 ~X~~X~	Active
Withdrawal Form completed	Participant withdrew consent			Yes		3 6 ~X~~X~	Active

APPENDIX Q: FORM UPR16 RESEARCH ETHICS REVIEW CHECKLIST

FORM UPR16

Research Ethics Review Checklist

UNIVERSITY OF PORTSMOUTH

Please include this completed form as an appendix to your thesis (see the Research Degrees Operational Handbook for more information

Postgraduate Research Student (PGRS) Information			**Student ID:**	UP716324
PGRS Name:	Dr Will Storrar			
Department:	SHSSW	**First Supervisor:**	Professor Anoop J Chauhan	
Start Date: (or progression date for Prof Doc students)				
Study Mode and Route:	Part-time ☒ Full-time ☐	MPhil ☐ PhD ☐	MD ☒ Professional Doctorate ☐	

Title of Thesis:	Temperature Controlled Laminar Airflow Traeatment for Patients with Severe Allergic Asthma
Thesis Word Count: (excluding ancillary data)	34,071

If you are unsure about any of the following, please contact the local representative on your Faculty Ethics Committee for advice. Please note that it is your responsibility to follow the University's Ethics Policy and any relevant University, academic or professional guidelines in the conduct of your study

Although the Ethics Committee may have given your study a favourable opinion, the final responsibility for the ethical conduct of this work lies with the researcher(s).

UKRIO Finished Research Checklist:
(If you would like to know more about the checklist, please see your Faculty or Departmental Ethics Committee rep or see the online version of the full checklist at: http://www.ukrio.org/what-we-do/code-of-practice-for-research/)

a) Have all of your research and findings been reported accurately, honestly and within a reasonable time frame?	YES ☒ NO ☐
b) Have all contributions to knowledge been acknowledged?	YES ☒ NO ☐
c) Have you complied with all agreements relating to intellectual property, publication and authorship?	YES ☒ NO ☐
d) Has your research data been retained in a secure and accessible form and will it remain so for the required duration?	YES ☒ NO ☐
e) Does your research comply with all legal, ethical, and contractual requirements?	YES ☒ NO ☐

Candidate Statement:

I have considered the ethical dimensions of the above named research project, and have successfully obtained the necessary ethical approval(s)

Ethical review number(s) from Faculty Ethics Committee (or from NRES/SCREC):	14/SC/0092

If you have *not* submitted your work for ethical review, and/or you have answered 'No' to one or more of questions a) to e), please explain below why this is so:

Signed *(PGRS)*:		**Date:** 18/05/2019

UPR16 – April 2018