Clinical Study Protocol

NCT01721291

Full Project Title:

Improving Inhaler Treatment and Small Airways Assessment in Chronic Obstructive Pulmonary Disease

Chief Investigator (Investigator accepting clinical responsibility):

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Informed consent / Undertake experiments / Data collection

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Undertake experiments / Data collection

Dr James Hull (Clinical Research Fellow)

Informed consent

All contactable at the above address of PI (see 1(a)).

1. Background/Rationale for this Study

Chronic obstructive pulmonary disease (COPD) is a global epidemic affecting ~10% of people aged >40years and currently the 5th commonest cause of death worldwide [1]. COPD is characteristed by chronic inflammation, but as there are no effective anti-inflammatory treatments, management focusses on using inhaled bronchodilators for symptomatic control, and short-acting β2-agonists are the drug-class most commonly used [2,3]. Inhaled medications form the cornerstone in the management of COPD patients. Approximately 38 million inhalers are dispensed in the UK/year [4]. However, current inhalers used in everyday clinical practice are inefficient, where at best, only 20% of the drug reaches the lungs [5]. Inhalers overcome their inefficiency and achieve clinical relief by using larger than needed drug doses given at the mouth, but importantly the greatly wasted part of the drug dose can give rise to adverse side-effects. Such inefficiency would not be accepted in other industries; e.g. washing machines that were inefficient and required 80% more powder, or inefficient car engines that required more fuel.

The small airways and lung parenchyma are the main sites of disease and airflow limitation in COPD [6]. This means the current inhalers in use, that were developed to treat asthma predominantly a large airway disease, may not be optimal in treating COPD patients. Poor delivery of inhaled bronchodilators to the peripheral airways may be a major factor limiting the clinical benefit provided by existing devices.The key to successful treatment could be to accurately target drug to the diseased sites.

However, very little is known about the fate of inhaled drug within the lungs of COPD patients. Importantly, there are no data on the regional lung deposition of inhaled bronchodilator and its relationship to clinical benefit or pulmonary function in COPD, mainly because there are inadequate functional parameters to sensitively assess the diseased small airways. The Pharmaceutical industry is currently advocating inhaled therapy to small airways in COPD with devices that; deliver drug slowly (tiotropium-Respimat™) [12]; have drug formulations of small particle size (BDP/formoterol-Fostair™) [13]; or deliver expensive drug in niche areas (e.g. inhaled α1-anti-trypsin for emphysema) [32]. There is a real need to actually determine whether targeting the regional small airways in COPD patients is indeed important, and what the physiological significance and clinical benefit is of small versus large airway targeting.

This research will use different inhaled β2-agonist particle sizes (small, intermediate, large) to target drug to different regional anatomical lung region in order to determine the ideal site of inhaled drug deposition in COPD patients and, using sensitive specialised physiology tests and pharmacokinetic methods, determine whether small versus large airways is of clinical benefit to patients.

2. Principal Research Hypothesis / Questions

The purpose of the study is whether by improving the efficiency in the lung deposition of inhaled bronchodilator drug (by varying the drug aerosol particle size), we can improve the physiological breathing responses of patents with COPD.

Q1. What is the lung deposition behaviour of inhaled bronchodilator aerosols of different particle size within the airways of patients with chronic obstructive pulmonary disease (COPD)? How does this distribution compare to that observed in healthy subjects with no lung disease?

Q2. What is the effect of different patient inhalation flows on the lung deposition of different sized bronchodilator particles? Is there a specific particle size and inhalation flow to achieve optimal lung deposition in COPD patients?

Q3. Does the regional deposition and distribution of inhaled bronchodilator aerosols influence the clinical (physiological pharmacodynamic) and systemic (urinary pharmacokinetic) responses in COPD patients?

3. Study Design

This protocol has two studies: Lung DEPOSITION study (in COPD patients and Healthy subjects) and Lung PHYSIOLOGY study (in COPD patients and Asthmatics).

Each study (Lung DEPOSITION and Lung PHYSIOLOGY) will be a randomised, double-blind, cross-over study (6 monodisperse 'fine-mist' aerosol treatments, controlled against one polydisperse 'coarse-mist' pressurised metered dose inhaler (pMDI) visit). Treatments will be given as one-off dose-administration. There will be an interval of at least 5 days between each study visit.

The Lung DEPOSITION study will involve radiolabelled drug treatments (monodisperse aerosols only = 6 visits). All the treatments in the LUNG PHYSIOLOGY study will be non-radiolabelled.

4. Study Outcomes

Primary outcome:

Lung DEPOSITION study: The primary endpoint for aerosol deposition is penetration index (PI) calculated from planar-images, which will indicate differences in regional lung deposition as a function of particle size.

Lung PHYSIOLOGY study: The primary endpoints are multi-breath nitrgen washout (MBNW) indices of acinar airways (Sacin) and conducting airways (Scond), which will indicate differences in small (and large) airway physiology as a function of particle size.

Secondary outcomes:

The secondary outcome measures for both studies are: analysis of the lung physiology (MBNW, Impulse oscillometry (IOS), spirometry, body plethysmography) and urine pharmacokinetics (urine 0-30minutes, 0-24 hours, 30mins -24 hours)

5. Study Centre / Number of Patients / Recruitment

The single-centre study will be carried out at the Asthma Lab, Royal Brompton Hospital and National Heart and Lung Institute, London, UK. Patients will be recruited from: Asthma Lab NHLI, Respiratory outpatients of the Royal Brompton and Harefield NHS Foundation Trust, St Mary's Hospital part of Imperial College NHS Trust, Local GP Practices and from our current patient Asthma Lab database from local GP Practices.

The study will recruit;

Lung DEPOSITION study: 12 mild-moderate COPD patients, 12 healthy subjects

Lung PHYSIOLOGY study: 26 mild-moderate COPD patients, 13 mild-moderate asthmatic patients

6. Inclusion criteria

COPD patients, either male or female, over the age of 40 with a clincal diagnosis of COPD with airflow obstruction (FEV1/FVC<0.7) and post-bronchodilator FEV1>50% predicted, gas trapping (on lung volume testing), and decreased carbon monoxide transfer factor.

Healthy subjects will be non-smokers (or ex-smokers stopped 5 years ago), will have no respiratory disease, normal spirometry and be age-matched to the COPD patients.

Asthmatic subjects, either male or female, over the age of 18 with a clincal diagnosis of Asthma with airflow obstruction (FEV1/FVC<0.7).

Capable of giving informed consent.

(ii) Exclusion Criteria

As a result of the medical interview, physical examination or screening investigations, the Physician Responsible considers the volunteer unfit for the study.

Oral corticosteroids taken within last month, as this can affect the breathing response and signifies that their condition needs to be controlled better.

Current involvement (or involvement in the last 4 weeks) in clinical trials assessing investigational medicinal products.

Previous adverse reaction to short or long acting β2 agonist.

Any subject with a contraindication to taking inhaled beta-2 adrenoceptor agonists (especially Salbutamol) as listed in the British National Formulary will not be entered into this study.

Those who have experienced an acute respiratory exacerbation requiring emergency room treatment and/ or hospitalisation within last four weeks as this signifies that their condition needs to be controlled better.

Pregnant or breast-feeding women.

Subjects unable to give Informed Consent.

7. Study Plan and Treatments (see also 'FLOWCHART')

All patients will receive all study treatments in each study. All treatments will be via the inhaled route of administration in each study. Treatments (all 'one-off' dosing) will only be taken while the patient is at the investigator site and there will be no treatments to take home with them.

Patients will randomly receive the following treatments (see also page 1 FLOWCHART document);

A) Lung DEPOSITION study

1. Salbutamol 1.5 micron-sized radiolabelled (*) aerosol particles at 30 micrograms single dose delivered via the spinning-top aerosol generator (STAG), inhaled at SLOW (20-40 L/min) inhalation by patient.
2. Salbutamol 3.0 micron-sized radiolabelled (*) aerosol particles at 30 micrograms single dose delivered via the STAG, inhaled at SLOW (20-40 L/min) inhalation by patient.
3. Salbutamol 6.0 micron-sized radiolabelled (*) aerosol particles at 30 micrograms single dose delivered via the STAG, inhaled at SLOW (20-40 L/min) inhalation by patient.
4. Salbutamol 1.5 micron-sized radiolabelled (*) aerosol particles at 30 micrograms single dose delivered via the STAG, inhaled at FAST (>60 L/min) inhalation by patient.
5. Salbutamol 3.0 micron-sized radiolabelled (*) aerosol particles at 30 micrograms single dose delivered via the STAG, inhaled at FAST (>60 L/min) inhalation by patient.
6. Salbutamol 6.0 micron-sized radiolabelled (*) aerosol particles at 30 micrograms single dose delivered via the STAG, inhaled at FAST (>60 L/min) inhalation by patient.
7. Salbutamol non-radiolabelled aerosol particles at 200 micrograms single dose delivered via a pMDI the STAG, inhaled at SLOW (20-40 L/min) inhalation by patient.

A) During the LUNG DEPOSITION study, participants will receive 6 treatments of 'fine-mist' monodisperse salbutamol of 1.5, 3.0 and 6µm micron sized aerosols radiolabelled with 99MTechnetium that will each be inhaled at a SLOW and a FAST inhalation flow by the patient (each treatment 30 microgram dose). Participants will also receive non-radiolabelled 'coarse-mist' inhaler of salbutamol from a pMDI (200 micrograms dose).'Fine-mist' monodisperse salbutamol aerosols will be generated using a spinning-

top disc aerosol generator (STAG) as previously described by Usmani et al (AJRCCM 2005). The operator will be blinded to the particle size being administered.

Following inhalation, participants will be seated in front of a gamma camera and inhaled particle distribution will be assessed with planar imaging. Scintigraphic images of the posterior thorax, anterior thorax, and lateral oropharynx will be recorded, in sequence, with the patient repositioned between views. This will be completed within 5 minutes following the aerosol inhalation. Subjects will undergo a krypton-81m ventilation transmission scan to define their lung boundary.

Participants will then undergo non-invasive measures of pulmonary function and pharyngeal function including; spirometry, impulse oscillometry, and multi-breath nitrogen washout test (at 30, 60 and 120 minutes post inhalation); body plethysmography (at 60 and 120 minutes); and pharyngometry (at 30 and 120 minutes).

Participants will be asked to void their urine 30 minutes post inhalation, which we will collect a sample of. Participants will also be asked to collect their urine over the next 24 hours. If there are unable to attend to hand-in their 24-hour urine sample the following day, our research staff will collect this 24-hour-urine sample from their house/workplace the next day. Urine collected will be frozen prior to analysis.

B) Lung PHYSIOLOGY study

1. Salbutamol 1.5 micron-sized *non*-radiolabelled aerosol particles at 15 micrograms single dose delivered via the spinning-top aerosol generator (STAG), inhaled at SLOW (20-40 L/min) inhalation by patient.
2. Salbutamol 1.5 micron-sized *non*-radiolabelled aerosol particles at 30 micrograms single dose delivered via the STAG, inhaled at SLOW (20-40 L/min) inhalation by patient.
3. Salbutamol 3.0 micron-sized *non*-radiolabelled aerosol particles at 15 micrograms single dose delivered via the spinning-top aerosol generator (STAG), inhaled at SLOW (20-40 L/min) inhalation by patient.
4. Salbutamol 3.0 micron-sized *non*-radiolabelled aerosol particles at 30 micrograms single dose delivered via the STAG, inhaled at SLOW (20-40 L/min) inhalation by patient.
5. Salbutamol 6.0 micron-sized *non*-radiolabelled aerosol particles at 15 micrograms single dose delivered via the spinning-top aerosol generator (STAG), inhaled at SLOW (20-40 L/min) inhalation by patient.
6. Salbutamol 6.0 micron-sized *non*-radiolabelled aerosol particles at 30 micrograms single dose delivered via the STAG, inhaled at SLOW (20-40 L/min) inhalation by patient.
7. Salbutamol non-radiolabelled aerosol particles at 200 microgram single dose delivered via a pMDI the STAG, inhaled at SLOW (20-40 L/min) inhalation by patient.

During the LUNG PHYSIOLOGY study (all treatments non-radiolabelled), participants will receive 6 treatments of 'fine-mist' monodisperse salbutamol of 1.5, 3.0 and 6µm micron sized aerosols each at a dose of 15 micrograms and 30 micrograms. Participants will also receive non-radiolabelled 'coarse-mist' inhaler of salbutamol from a pMDI (200 micrograms dose).'Fine-mist' monodisperse salbutamol aerosols will be generated using a spinning-top disc aerosol generator (STAG) as previously described by Usmani et al (AJRCCM 2005). The operator will be blinded to the particle size being administered.

Following inhalation, participants will undergo non-invasive measures of pulmonary function and pharyngeal function including; spirometery, impulse oscillometry, and multi-breath nitrogen washout test (at 30, 60 and 120 minutes post inhalation); body plethysmography (at 60 and 120 minutes); and pharyngometry (at 30 and 120 minutes).

Participants will be asked to void their urine 30 minutes post inhalation, which we will collect a sample of. Participants will also be asked to collect their urine over the next 24 hours. If there are unable to attend to hand-in their 24-hour urine sample the following day, our research staff will collect this 24-hour-urine sample from their house/workplace the next day. Urine collected will be frozen prior to analysis.

8. Study Procedures (see also 'FLOWCHART')

Lung volume tests:

Spirometry/Reversibility is a type of lung function test that involves breathing into a mouthpiece. It measures the amount of air that can be exhaled in one second as well as the total volumeof air in th elungs. The results provide information on lung volumes and on their function. This test takes ~2 minutes. Reversibility is a test that measures how easily the air tubes open up when they are given a reliever inhaler (bronchodilator) such as Salbutamol.

'Body Box' (Plethysmography) is a type of lung function test. Subjects will be asked to sit in a see-through plastic, airtight box (the size of a large 'lift' or 'elevator'), where they will breathe gently and normally. The movement of their chest will be detected by the machine which will calculate the volumes of their lungs and pressures ('resistance') of the airway tubes. This test takes ~5 to 10 minutes.

Acoustic Pharyngometry. This test uses sound waves (similar to a ship's ultrasonic−sonar) to measure the dimensions of the throat. The test takes 1 minute.

Small airways tests:

Impulse Oscillometry (IOS) measurements. Subjects will be asked to breathe gently and comfortably through a mouthpiece while wearing nose clips. The mouthpiece is connected to a loudspeaker which generates sound and pressure waves (a bit like a ship or submarine's sonar waves), which go into the lungs and are reflected back up to the mouth. A computer calculates the pressures ('resistance') in the air tubes. This test takes ~2 minutes.

Multiple Breath Nitrogen Washout (MBNW). Subjects will breathe gently and comfortably through a mouthpiece, which is connected to a blowing machine which measures nitrogen. From the gas breathed out, we can estimate how narrow the small airways and large air tubes are. This test takes ~10 minutes

Lung imaging: (in the LUNG DEPOSITION study only)
Inhalation of Krypton Gas. We will subjects to inhale a few breaths of Krypton gas. This takes 2 minutes at most and there is no taste or unpleasant feeling.
Planar Gamma Camera Imaging. We will subjects to be seated upright on a chair in front of the gamma-camera for 5 minutes after inhaling the treatment, during which time an image of their lungs will be taken

Urine tests:
We will ask subjects to provide a sample of their urine at 30 minutes after inhaling the treatment, to assess how much of the inhaled treatment has deposited in the lungs and then reached the rest of the body. After finishing this Study Visit and leaving the Department, we will ask subjects to collect their urine into a container for the next 24 hours. (We will provide subjects with a suitable collection vessel for their urine samples and a larger storage vessel into which they will be able to transfer all their urine samples). If subjects are unable to attend to hand-in their 24-hour urine sample the following day, our research staff will collect this 24-hour-urine sample from their house/workplace the next day.

9. Screening and Study Visits

Screening visit:

- Informed Consent of every subject will be obtained by one of the Study Team Investigators [see section 1(b)] before any study procedures are done
- The subject's medical and smoking history, current medications will be documented in the hospital notes and case report form
- Spirometry will be performed at screening to determine eligibility for the study and all inclusion (section 6(i)) and exclusion criteria (section 6(ii)) assessed.
- For eligible subjects, if patients are currently prescribed Salbutamol as their 'rescue' inhaler, then this will be changed to an identical drug called Terbutaline, until they complete this research study. This will enable subjects to continue using their 'rescue' medication as they need it, because our urine measurements cannot separate Salbutamol delivered by their own regular blue 'rescue' puffer, from the Salbutamol we will deliver by our special 'fine-mist' nebuliser in the study.

Study Visits:

We will ask patients to abstain from alcohol one day before the Study Visits and for 24 hours after receiving the study treatment. In the 6 hours before each Study Visit, we will also ask patients not to use either their Terbutaline, Salmeterol (also known as a Serevent® or Seretide®), Eformoterol (also known as Oxis® or Symbicort®), Ipratropium (also known as Atrovent®) or Tiotropium (also known as Spiriva®) (if they

are prescribed these), unless patients feel they need them. There will be no change or addition to patients' treatment throughout this study by us.

There will be a minimum of a 5 day washout period between study periods.

At the Asthma Lab, subjects will be asked about any adverse effects they may have experienced. If so, the necessary action (see Section 10 below) will be undertaken). Spirometry will also be done and patients will be required to be within +/-15% of baseline Screening values before commencing study medication, to ensure lung variability is minimised.

10. Medication/IMP

Supply of drugs

The study drugs will be supplied by Royal Free Hospital (RFH), London UK to the Pharmacy of the Royal Brompton Hospital where they will be stored and dispensed.

RFH Pharmacy will assign labels to all study medication in accordance to the protocol and ICH GCP. The labels on the packages and unit medication will specify all necessary information for a correct identification of the medication boxes and individual medication units.

All study medication accountability will be performed at the Royal Brompton Hospital by members of the study team and returned /unused medication will be destroyed by the Royal Brompton Hospital Pharmacy at study closure.

An independent scientific investigator will create a computer generated randomisation lists for the study in accordance with the protocol. Code break envelopes will be provided with copies of the randomisation code, which will be stored in the RBH Pharmacy.

11. Sample Size and Statistical Analysis

Determination of sample size

Aerosol deposition. Based on penetration index (PI) data from my previous particle-size deposition study [27], n=12 subjects will have 97% power (1-β) to detect a clinically relevant difference in means of 0.19 for PI, assuming a standard deviation of differences of 0.15, using a paired t-test with a 0.05 two-sided significance level (α). We do not have previous within patient repeatability data for PI for each individual particle size, as it is unethical to expose patients to more radioactivity than is needed. However, our data were highly significant ($p < 0.001$) in differences of PI between the three particle sizes (1.5-, 3-, 6-μm) that correlated with clinically significant differences in bronchodilator responses, and we have used the within subject SD data for PI (collectively of all 3 particles given to each patient), in the sample size calculation.

Small airway physiology. Based on Sacin and Scond data [Verbanck 1999], where MBNW responses in COPD and asthma were measured before and after pMDI salbutamol (corresponding to ΔFEV1 19% - a clinically important difference), we calculate n=14 subjects will have 90% power (1-β) to detect a clinically relevant difference in means of 0.027 for Scond, assuming a standard deviation of differences of 0.022, using a paired t-test with a 0.05 two-sided significance level (α). Allowing for inherent biological variability for repeated measures over time, the reported intraclass correlation of Scond and Sacin is

0.84, 0.95 respectively [Verbanck 1999], and so the sample-size required for airway physiology analysis in COPD patients is n=26 (Stata-10, Statacorp, Texas, USA).

Statistical methods

Longitudinal analysis of paired-data will be performed within and between different groups. Data from the primary and secondary endpoints will be use to test the null hypothesis using two-way parametric analysis of covariance (ANCoVA), with factors for subject, treatment period and order. Modified paired t-tests will be undertaken using the Bonferroni method to adjust for P values and multiple comparisons between the three particle sizes. Lung deposition comparisons will be made to assess particle size deposition effects within diseased COPD patients, within healthy subjects (HS) and between disease (COPD) and health (HS). Comparisons will be made to determine the effects of inhalation flow on regional lung deposition of the three particle sizes in COPD and HS. Small airways physiology comparisons will be made between monodisperse aerosols of different particle size in COPD patients and between monodisperse and polydisperse-MDI aerosols.

12. Adverse Events

An **adverse event** (AE) is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings).

In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or wash-out periods, even if no study treatment has been administered.

A **serious adverse event** (SAE) is an AE occurring during any study period (i.e., run-in, treatment, wash-out, follow-up), and at any dose of the investigational product, comparator or placebo, that fulfils one or more of the following criteria:

- results in death
- is immediately life-threatening
- requires in-patient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect
- is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above

A distinction should be drawn between **serious** and **severe** events. A severe event is a major event of its type. The term “severe” is used to indicate the intensity of a specific event, while the term “serious” is based on patient/event outcome or action criteria.

A **suspected unexpected serious adverse reaction** (SUSAR) is any adverse event with a reasonable possibility of a link to the study drug that is both serious and unexpected (i.e. not consistent with the information about the study drug in either the SPC or IB).

Procedures for Serious Adverse Event Reporting

The Chairman of the Ethics Committee, Imperial College Clinical Joint Research Office (JRO) and the Sponsoring Consultant will be immediately informed about all serious untoward events.

It will be the responsibility of the Principal Investigator and Study Team Investigators to report all adverse events (both serious and non-serious).

Depending on the nature of the event, the reporting procedures will be as follows:

- **All Adverse Events** occurring during the clinical investigation will be recorded and documented in the relevant section of the Case Report Form (CRF)
- **Serious Adverse Events** will be documented immediately on a standard narrative form and will be reported as soon as possible to the Chairman of the Ethics Committee and to Senior Administrator.

Expedite Reporting will be performed by the Principal Investigator in case of any **suspected, unexpected, serious adverse reaction (SUSAR)** or in case of other safety issues that qualify for expedite reporting, in accordance with the European Directive 2001/20/EC.

The expedite reporting to the Competent Authority and Ethics Committee will be performed as follows:

- fatal or life-threatening SUSAR, will be reported as soon as possible but no later than **7 calendar days** after first knowledge of the minimum criteria for expediting reporting. Relevant follow-up information will be completed as soon as possible and sent within an additional 8 calendar days.
- non fatal or life-threatening SUSAR, will be reported as soon as possible but no later than **15 calendar days** after first knowledge of the minimum criteria for expediting reporting.

Copy of SAE/SUSAR reporting will be notified by the Principal Investigator to Imperial College Clinical Research Office within the same timeframe.

13. Indemnity

Indemnity will be provided by Imperial College Indemnity Scheme which has been arranged through the Joint Research Office (JRO) at Imperial College. Imperial College's Miller 'no fault' clinical trials policy: number PIMP00511. Public Liability cover is also provided for Imperial College under this policy reference number.

14. Data Handling & Record Keeping

Hard copies of participant's trial research files will kept under lock and key in the Asthma Laboratory, Royal Brompton Hospital. Access to these will be limited to the Respiratory Physician conducting the study (Dr Omar Usmani), Study Team Investigators and the Clinical Research Nurse (Ms Sally Meah). All files will have non identifiable information, that is, each participant will only be identified by a study code and the study codes for each participant will be kept in a separate locked cabinet. The Investigators will permit trial-related monitoring, audits, IRB/IEC reviews and internal and external regulatory inspection with provision and direct access to source documents and data.

The following has been included in the Consent Form to patients;

"By agreeing to take part in this research study you will be allowing certain persons to see the information about you. Your information will be looked at to confirm that it is correct and that it is related to you and that the study is being carried out correctly. This will be done by selected people working for Imperial College and organisations acting on behalf of Imperial College London, such as the local ethics committee, and the government regulatory authorities. These persons are required to maintain the confidentiality of your information. This is to meet legal or regulatory requirements for the study and to ensure that we are carrying out this research study to recommended guidelines on good research practice. It is intended that the collective results and data from the research will be publicly available in an anonymous form in peer reviewed scientific journals and conference presentation. Maintaining your confidentiality is important to us. Your personal information (for example, your gender, age, and the details of your medical conditions) and other information (the data collected as part of the study) will be identified by letters and numbers (that is, coded). Imperial College London will keep the information and the results collected about you in this study in a secure place. Your information will be processed electronically (that is, by a computer) or manually and analysed to determine the outcome of this study. Imperial College London may use your information for other medical/health care purposes related to this study. For this purpose only coded information will be used. These data may be used for:

- Administration purposes
- Research and development of pharmaceutical products
- Diagnostics and medical aids
- Statistical analysis

You have the right to ask the study Doctor about the data being collected on you for the study and about the purpose of this data. You have the right to ask the study Doctor to allow you to see your personal information and to have any needed corrections to it made.

It is intended that the results of this study will be published in a Medical journal and may be presented at Medical conferences in the UK and abroad, but your identity will not be revealed, nor will your name appear in any publications, reports or slides, produced from the results of this research study. Should you request any

information on the publication of this study, the study Doctor will be able to tell you where the results are published, when the study is finished. "

It will be the responsibility of the Chief Investigator and Consultant Respiratory Physician conducting the study − Dr Omar Usmani, to ensure the well−being of all participants and that they are able to contact him for any queries regarding the study. Dr Usmani & Ms Sally Meah will also be responsible for the daily management and monitoring of the research data and management of the staff involved with the research. Dr Usmani & Ms Sally Meah will liaise with the clinical research governance office at Imperial College with respect to auditing the research study. Overall responsibility for the study lies with the Chief Investigator, Dr Omar Usmani, Clinical Senior Lecturer and Honorary Consultant in Respiratory Medicine, National Heart and Lung Institute, Imperial College. The project will be registered with the Clinical Research Office of Imperial College London and has been registered with **ClinicalTrials.gov**

15. Publication

It is hoped that the results and data from the research will be available publicly in peer-reviewed publications. Although no specific publications will be produced for the research participants, should a participant request feedback on the outcome of research towards which they have contributed, this will be provided to them. Information about publication arrangements will be included in the participant information sheet, as well as a statement regarding information on individual requests for feedback on the study results.

16. Ethics and Amendments to the Protocol

Ethics review

The final protocol and the final version of the written informed consent form must be approved or given a favorable opinion in writing by an independent ethics committee (IEC). The principal investigator(s) is responsible for informing the IEC of any amendment to the protocol in accordance with local requirements. The principal investigator(s) must also provide the IEC with reports of serious adverse events from the study site as per local requirement.

Patient information and consent

The Principal Investigator(s) will ensure that the patients are given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patients should be given the opportunity to ask questions and allowed time to consider the information provided. The patient's signed and dated informed consent must be obtained before conducting any procedure specifically for the study.

All patients will be requested to provide their informed consent prior to any study-related procedures. If the patient is unable to provide written consent immediately, oral consent should be witnessed in writing by a patient representative (i.e. legal guardian,

accompanying person or hospital staff not directly involved in this study). In this case, the patient should sign the written consent as soon as possible, at the latest before the end of the study.

The principle investigator(s) must store the original, signed written informed consent form and a copy must be given to the patient.