PARTICIPANT INFORMATION SHEET

Epigenetics of Severe Asthma Study

Introduction

You are being invited to enrol in the *Epigenetics of Severe Asthma* study. Please take time to read the following information carefully and ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Thank you very much for reading this.

What is the purpose of this study?

Asthma is a condition that affects the airways, which are tubes that carry air in and out of the lungs. People with asthma tend to have sensitive airways that can react to any triggers, e.g. cold air, dust and pollens, causing tightening of their airways. They also have inflammation of the smaller airways. People with asthma can have varying forms of the condition from mild or moderate to severe disease. Those with mild asthma can experience fewer daily symptoms with lower levels of treatment and have less healthcare use. On the other hand, people with severe asthma can experience significant disability from their disease, rely heavily on medical support and need high levels of treatment that can sometimes cause unwanted side-effects. It is unclear why some people experience such severe disease while many others have milder asthma. However it is clear that the development of asthma appears to be driven by the combination of inherited factors that we have in our genes and the environment in which we live. 'Epigenetics' is a process that determines how the function of cells is regulated in response to external influences in its environment. During this process there are minor alterations in the structure of the DNA (short for deoxyribonucleic acid), but not the DNA code (sequence), which determine if the genes are switched on (active) or off (dormant) within cells. These changes can be detected using cutting-edge technologies which allow detailed assessments of genes and their individual components such as DNA and RNA (ribonucleic acid). We know that epigenetic changes can determine health and disease. Research has begun to show that these epigenetic mechanisms are relevant to asthma. It remains to be seen whether different epigenetic mechanisms are responsible for more severe asthma compared to milder asthma. In this study we will explore whether that is the case or not by studying epigenetic markers obtained from samples provided by people with both severe and mild asthma. These samples include blood, sputum (phlegm) and in a small number of people airway samples taken through a test called a bronchoscopy. If we can understand what causes people to develop more severe asthma we may in future be able to identify at risk people at an early stage, develop better treatments for severe asthma or even understand how to prevent certain types of severe asthma from developing.

Why have I been chosen?

You have been chosen because you are either

a) A participant in the WATCH (Wessex AsThma CoHort of difficult asthma) Study and have a form of "severe asthma".
b) A participant in the Isle of Wight Birth Cohort (IOWBC) Study and have a form of "mild asthma".
c) Someone who is known to have "mild asthma".

What will happen to me if I take part and what do I have to do?

If you agree to take part in this study you may need to attend at the Research Centre on 2-3 occasions over about 9 months. If you live on the mainland all of the required visits will be at Southampton General Hospital. If you live on the Isle of Wight 1 of these visits would be at the David Hide Asthma & Allergy Research Centre, Newport, Isle of Wight and 1-2 will be at Southampton General Hospital.

Visit 1:

At the 1st visit a member of the study team will discuss the nature of the study with you to make sure that any questions that you have are answered. If you are happy to proceed you will be asked to sign a consent form. This visit will take approximately 30 minutes of your time.

Blood Sample:

A sample of approximately 50mls of blood will be taken (under 1/7th of a blood donation, or 8 teaspoons) to assess epigenetic and genomic factors. If you request, a small amount of local anaesthetic cream will be applied to your skin to minimise any discomfort. Your body will replace the blood in a very short time. If you have taken part in the WATCH or IOWBC studies then you may be required to update a lung function test and complete a simple asthma-related questionnaire at this visit.

In some participants 1 unit (~470mls) of blood will be requested for more extensive immunological and genomic studies. To investigate how certain allergens cause allergic asthma, we need to isolate and study those immune cells that specifically respond to this particular allergen. These immune cells are very rare in the blood, but do play a critical role in allergic asthma. Therefore, to study these rare but important cell types using cutting-edge genomic tools, we would require 1 unit of blood. This volume of blood is routinely obtained from regular blood donors every 8 weeks.

Other Tests:

If you have not previously participated in the WATCH or IOWBC studies then we would like to undertake a few further assessments at this visit so that we can ensure that we have collected similar information about you and your asthma compared to participants who are already part of these studies. This may take up to an additional 60 minutes of your time. These include;

1. *Questionnaires*

These standardised research tools enable us to collect information about the nature of your asthma and factors relevant to that. Most of the data we need will be obtained from answers you give us to these questions. In addition, relevant information relating to your GP's care of your asthma will be incorporated from the Hampshire Health Record or other comparable GP Record System.

2. *Skin Prick Allergy Tests*

If you agree, drops of 13 common allergens will be placed on the skin and pricked to see what you are allergic to. Your arm might itch or become red at the site where the test was done and there may be mild discomfort from the needle prick.

3. *Blood Tests*

If you agree, a panel of blood tests consistent with that taken in the WATCH study will be taken to assess relevant immunological and biochemical tests in relation to your asthma.

4. *Exhaled Nitric Oxide*

Nitric oxide is a gas present in everyone's breath. You will be asked to exhale into a mouthpiece, breathing out at different speeds. By doing this the nitric oxide content of your breath will be measured by a computer. This will measure the inflammation in your airways.

5. *Spirometry*

This is a test to measure the amount of air you have in your lungs by breathing in and how well you can push the air back out by blowing it hard into a tube.

Visit 2:

All study participants will be invited 6-9 months after visit 1. At this visit you will undergo a procedure called a sputum induction test and provide a 2nd blood sample of similar size to that in visit 1. Both tests are being done to obtain samples for further epigenetic and genomic assessments. The blood test is being repeated to find out whether the findings from visit 1 are stable over time.

This visit will happen at the Wellcome Trust Clinical Research Facility at Southampton General Hospital or at the David Hide Asthma & Allergy Centre, Isle of Wight at a time that is convenient for you. The whole appointment will take approximately 2 hours. Participants undergoing the sputum induction test will be reimbursed for travel expenses and car parking cost at the Departmental rate.

What is a sputum induction test?

This is a simple test that involves producing a fresh sample of sputum to be analysed in a laboratory.

What should I do before the test?

Please inform the Research Team (telephone number at the top of your appointment letter) if any of the following apply to you;

- If you have coughed up any blood in the last 2 months.
- If you have been told by your Doctor that you have a collapsed lung
- If you have used a GTN spray in the last 2 months, for chest pain.
- If you have been told by a Doctor you have a blood clot or you have had a heart attack in the last 2 months.
- If you have recently (within the last 4 weeks) had a chest infection requiring antibiotic treatment.
- Any surgery in the last 2 months (including eye surgery).
- If you feel unwell on the day of the test.

Important instructions

- Please do not smoke for 4 hours before the test.
- Please do not drink alcohol for 4 hours before the test.
- Please do not partake in any vigorous exercise 30 minutes before the test.
- Please do not eat a substantial meal 2 hours before the test.

What happens during the test?

Before the test starts the Research Team will explain the test to you in detail and will answer any questions that you may have regarding it. This is a painless procedure. It involves breathing in a mist of concentrated saline (mild salty water) through a nebuliser and then performing cough-like movements to produce a sample of sputum. At the beginning of the test you will be required to perform a breathing test (spirometry) to measure your lung function. You will then be given 2 puffs of salbutamol (Ventolin; the blue inhaler) to breathe and after 15 minutes the breathing test will be repeated. After that you will be given the salty mist to breathe for 5 minutes at the end of which you will be asked to have a deep cough and spit any phlegm into a dish for collection. Your breathing test will then be repeated. If your lung function falls by more than 20% the procedure will be stopped and you will be given 4 puffs of the salbutamol to relieve any chest tightness. Otherwise you will be asked to repeat this cycle of breathing the salty mist and coughing up a phlegm sample 3 more times at 5 minute intervals as long as your repeat breathing tests do not fall by more than 20%. If at any point your breathing test falls by more than 20% the sputum induction test is stopped and you will be given salbutamol as above.

What happens after the test?

After the test you will be kept under observation until your breathing test is within 95% of the value at the start of the test to make sure you are fit to go home.

What are the risks and discomforts?

This test aims to make you cough up a sputum sample so may cause temporary discomfort due to the coughing. A small number of asthmatic people undergoing this test may experience some chest tightness or wheeze which is why your lung function is repeatedly measured by a breathing test during the procedure. If your breathing test shows a significant drop the test will be stopped and you will be given some salbutamol to relieve any discomfort.

Visit 3 (Optional):

This visit is optional where smaller subgroups of study participants will be selected and invited to attend 1 or even 2 of the following optional or additional visits during the 6 to 9-month period after visit 1. We will select and invite the following subgroups of study participants:

a) Participants who have required a course of oral steroids (Prednisolone) for an asthma flare up during the study period. This will exclude participants who take oral steroids for their asthma on a daily basis.

b) A small subgroup of participants with severe and mild asthma who have good asthma control, have not had an asthma flare up in the previous 4-6 weeks that required a GP visit or hospital admission, and are not taking any blood thinning medications (e.g. anticoagulants including Warfarin, Clopidogrel, Rivaroxaban, Apixaban or Edoxaban) will be invited for bronchoscopy testing (see Visit 3b section for detail)

c) Participants who have subsequently been started on an injectable biological asthma treatment (e.g. Omalizumab or Mepolizumab) during the study period.

The following sections below provide a detailed explanation of the additional and optional *visits 3a, 3b and 3c* which you may be invited to:

Visit 3a: Additional Visit to Assess Impact of Oral Steroid (Prednisolone) on Findings

It is unknown how treatment may alter the influence of epigenetic factors upon asthma. To assess that further in this study we would like to take a further 50ml blood sample should you have to take a course of prednisolone tablets due to a flare up of your asthma during the 9 month duration of the study. You will therefore be invited to inform the research team if that situation arises and they will then make arrangements for you to provide that blood sample if you are happy to do so.

Visit 3b (Optional): Bronchoscopy Test

A small subgroup of study participants (i.e. 15 with severe asthma and 15 with mild asthma) whose asthma is controlled and been stable for 4-6 weeks prior to this visit will be invited to undergo a bronchoscopy to directly obtain airway samples for our research. If you agree to have this further test it will happen at the Wellcome Trust Clinical Research Facility at Southampton General Hospital at a time that is convenient for you. This visit will take approximately 3-4 hours of your time. In view of the time and effort involved with this procedure, participants undergoing bronchoscopy will be reimbursed for their time, as well as travel expenses and parking cost.

What is a bronchoscopy?

A bronchoscopy is a routine diagnostic test which allows the doctor to pass a small fibreoptic telescope through the nose to the back of the throat and down the trachea (windpipe) to examine the large airways of the lungs. A tiny pair of forceps can be passed into the lungs to take samples. These will be analysed to help determine the cells and molecules involved in Asthma and Allergy. It is normally a very safe and well tolerated procedure.

How do I prepare?

You will need to attend the Wellcome Trust Clinical Research Facility usually at 9am having fasted (not had anything to eat or drink) for at least 4 hours prior. You can take your inhalers as normal and any essential medications 2 hours before with a small sip of water. If you are unsure of what to do regarding any of your medications you should discuss this with the nurse or doctor at the initial visit or telephone us for advice. Please bring your inhalers and medications with you. If you are unwell in the week before the procedure is scheduled, please contact a member of the research team to see if it should be rebooked.

What happens before and during the procedure?

Prior to the procedure we will insert a small plastic tube (cannula) into your hand or arm and use this to give you medication to make you feel drowsy (Midazolam) and reduce coughing (Alfentanyl). In addition to this we will spray your nose and the back of your throat with anaesthetic spray to numb them so that they are not irritated by the procedure. This preparation takes up to 15 minutes, the anaesthetic tastes unpleasant and may make you cough but this passes off quickly. We will be monitoring your heart rate, blood pressure and oxygen levels throughout this time. We then pass the bronchoscope down one of the nostrils, through the voicebox and into the main airways of the lung, giving more anaesthetic spray on the way. Some people have small nasal passages and in these circumstances we pass the bronchoscope through the mouth.

After inspecting the airways we would take some samples. There are 3 types.

1. Lavage/Wash – a small amount of fluid will be flushed into a corner of the lung and then sucked out again. This will allow us to collect free cells within the airways. You may get a taste of salty water in your mouth.
2. Brushing – a small brush will be gently rubbed against the airway wall to remove some cells.
3. Biopsy – small forceps are used to sample the airways – there are no nerve endings here so this is not painful. Up to 10 biopsies may be taken, about 1- 2mm in size, smaller than a pin-head.

This part of the procedure will take 20-30 minutes on average. With the sedating medications some people go off to sleep while others are pleasantly drowsy. If you wanted us to stop the procedure at any time we would do so.

What happens after the procedure?

After the procedure you will be kept under observation for 2-3 hours. During this time you will be checked regularly by our experienced bronchoscopy nurses. If necessary we may give you nebulised Salbutamol or a course of steroids. After 2 hours you will be allowed to have something small to eat and drink and then discharged home. There is a very small chance that you might need to stay for longer or overnight. As you have been given a sedative you will need a responsible friend or family member (over 16) to accompany you home. You should not drive or operate heavy machinery for 24 hours after the procedure. We would also advise against drinking alcohol for 24 hours after the procedure.

What are the risks and discomforts?

It is very common to cough up small flecks of blood for the 48 hours after a bronchoscopy. This is nothing to worry about. If it persists longer than this you should contact a member of the research team.

Common risks

- Local discomfort – sore throat or sore nose during or after the procedure
- Fever/chills
- Dizziness after the sedative injection
- Mild chest pain (10 in 100)
- Temporary worsening of asthma requiring steroids (20 in 100)
- Pain or infection at cannula site (1 in 100)

Uncommon risks (less than 1 in a 1000 procedures)

- Bleeding
- Spasm of major airways/vocal cords
- Infection (pneumonia/bronchitis)
- Irregular heartbeat

Very serious risk (extremely low)

Many thousands of research bronchoscopies have been performed safely worldwide and the risk of death is extremely remote. Of the thousands of research bronchoscopies performed at University Hospital Southampton, no deaths have been reported. Indeed to date, no deaths have ever been reported for this procedure anywhere in the UK. However, one death was reported after a research bronchoscopy in the US.

The doctor performing the bronchoscopy will talk to you beforehand about the risks outlined above and how these relate to your own medical conditions and health. If clinically relevant information is obtained at the time of the bronchoscopy this will be shared with you and the relevant doctors involved with your care. Otherwise the samples obtained will be anonymised and the results will not be put in your medical records.

Visit 3c: Additional Visit to Assess Impact of Biological Asthma Treatments on Findings

A small subgroup of study participants starting any approved injectable biological treatment (e.g. Omalizumab or Mepolizumab), as part of their standard care, during the study period will be invited, 6-9 months after visit 1, to provide an additional 50mls blood sample. This is to assess the effects of such treatment on the epigenetic and genomic factors. If you request, a small amount of local anaesthetic cream will be applied to your skin to minimise any discomfort. Your body will replace the blood in a very short time.

What are the possible disadvantages and risks of taking part?

The possible disadvantages and risks of each of the tests which you may be asked to participate in have been detailed in this information sheet.

What are the possible benefits of taking part?

There may not be a direct individual benefit from the ‘additional tests’ which will occur if you choose to take part, except in the knowledge that you are providing information that will help better understand more severe asthma and may help in developing new therapies for asthma.

Do I have to take part?

The study is purely voluntary and there is no need to participate if you don’t wish too. Not taking part will not affect your ability to be seen in the clinic.

What if there is a problem?

We do not anticipate there being any problems that would specifically relate to this study. All the information used in this study is obtained from questionnaires and tests that you have had through your involvement in either the WATCH or IOWBC studies. Similar information will be gathered from participants with mild asthma who have been invited to the study from the community.

Will my taking part in the study be kept confidential?

All details of your participation in this study will be confidential and only members (doctors, nurses and other allied health professionals) of the Research Team will have access to your medical records. All stored samples will be coded and cannot be identified directly as being related to yourself by anyone handling the samples for analysis.

Who will have access to my health records?

The personal information collected in this study will be kept confidential. The data we collect from you will not be labelled with your personal details and will be stored securely. Data collected during the study may be shared with our research collaborators; however they will not know who the information belongs to as it will be coded to make it anonymous. Only the study personnel or your clinical team will have access to your personal details. Data may need to be shared with the sponsor (University Hospital Southampton NHS Foundation Trust) of the study as part of their legal monitoring activities. You will not be individually identified in any reports or publications resulting from the study.

Involvement of your General Practitioner (GP)

With your permission we will inform your general practitioner that you have agreed to take part in this study.

What will happen to any samples I give?

The blood, sputum and (if appropriate) bronchoscopy samples that you provide will be tested for epigenetic markers that may be associated with severe asthma. Some analyses will be conducted in our own laboratories but the majority will be conducted with our collaborators at the La Jolla Institute for Allergy and Immunology, San Diego, USA. In some circumstances we may collaborate with other outside investigators who are able to conduct further analysis that will improve our understanding of the causes of severe asthma. These collaborators may be working in other hospitals or Universities (Academic collaborators) or may be working for Pharmaceutical companies (Industrial collaborators). When we collaborate with outside investigators your samples will only be identified with a number and will not be directly traceable to you.

Will any genetic tests be done?

Genetic studies will be carried out to improve our understanding of how genes influence the development of asthma. Any genetic analyses conducted will be unlikely to produce results that have any relevance to you as an individual but will help us to develop fresh ideas that hopefully will improve our ability to develop new treatments in the future. We would also like to store any samples collected for future research in asthma.

Genomic studies examine genetic differences across the human genome (set of human genes). Researchers study the association between genes and health conditions or personal

characteristics like vision, obesity, or behavioral traits. In this part of the study we will be collecting information about the individual genes from your whole genome. We will use this information for our study objectives and it will not be shared unless you agree to this during the consent process. In addition, if you agree, the data will be entered into external scientific databases so that it can be broadly shared with other researchers performing other genomic studies. For example, the National Institutes of Health (NIH, an agency of the US federal government) maintains a database called "dbGaP." Databases like this serve as a repository of all kinds of genomic data from studies funded by the NIH and conducted in the US and around the world. The aim of collecting this information in a repository is to allow qualified researchers to look for genetic connections for a range of topics in the future. The information may be used to learn if certain genes are associated with certain traits, diseases and/or treatment effects. Making data broadly available in this way, means that your contribution and the data generated in this study could be helpful in advancing other areas of scientific research.

Traditionally used identifying information about you (such as name, phone number, address) will NOT be included in these databases or shared with others. De-identified genomic data generated in this study may be deposited in databases that will be publicly accessible via the Internet. Researchers with an approved study may access and utilise your de-identified genetic, genomic and/or health information deposited in the database (dbGAP) after approval by the regulatory authority (NIH). Strict safety measures are in place to protect the privacy of your information. However, because your genetic information is unique to you, there is a small chance that someone could trace it back to you or your family. The risk of this happening is very small, but may grow in the future. Researchers will always have a duty to protect your privacy and keep your information confidential.

You may withdraw consent for research use of genomic data or health information at any time. In this event, data will be withdrawn from any repository, if possible, but data already distributed for research use will not be retrieved.

The consent form for the study is split into two separate parts so if you want, you can consent to the genetic studies but not the genomic data sharing part of the study. If you decide to do this it will not affect your participation in the main part of the study.

What will happen to the results of the research study?

We aim to publish the results of the study in medical journals so that other doctors and researchers can make use of them. Such publications may result in an article in a local paper. We also aim to provide a simple summary of the study and results, which will be fully accessible to the public, on the David Hide Asthma & Allergy Research Centre website: http://www.allergyresearch.org.uk/
It will not be possible to identify any individuals involved in this study from these published results.

How long will my health information and genetic/genomic data be stored for?

Your personal information and health data (paper and electronic based information) will be stored in a secure archiving facility in the Faculty of Medicine, University Hospital Southampton for a minimum period of 15 years following the end of the study. This is in accordance with the Data Protection Act 1998 and NHS England Confidentiality Policy 2016. After this time period, the information will be destroyed. Your de-identified genetic/genomic data will be stored for longer as this will NOT contain any of your personal or health information.

Who is organising and funding the research?

This Study is organised by the Clinical Experimental Sciences Department, Faculty of Medicine, University of Southampton in conjunction with the La Jolla Institute for Allergy and Immunology, San Diego, USA and the David Hide Asthma & Allergy Research Centre, St Mary's Hospital Isle of Wight. The Study is funded by the NIH (National Institutes for Health), USA.

Who has reviewed the study?

The study has been reviewed by an ethics committee (NRES 18/SC/0105, ethics no. 237109) and by the Research and Development department at University Hospital Southampton and St Mary's Hospital, Isle of Wight.

How long do I have to decide whether I should take part?

Your decision to participate in this study is entirely voluntary. You should take as much time as you need.

Will I be reimbursed for my time and travel?

Reasonable travel expenses and parking costs you (and your escorting family member or friend) may have incurred as a result of participation in this study will be reimbursed at standard Departmental rates. Participants who undergo bronchoscopy will be reimbursed for their time, as well as travel and parking expenses as explained on the information sheet. The study team will discuss this with you.

I have concerns/a complaint over the conduct of the study/the investigators/the clinic, whom should I contact?

If you feel you are able to raise those concerns with your respiratory doctor or a member of the nursing team (research or clinical), please do so and we will endeavour to address them. If you would prefer to speak to an independent body, the Patient Advice and Liaison Service (PALS) can be contacted on 01983 534850, at pals@iow.nhs.uk, at the information point just inside the main entrance to the hospital, or at the following address: Patient Advice and Liaison Service, A Level, St Mary's Hospital, Parkhurst Road, Newport, Isle of Wight, PO30 5TG.

Thank you for taking time to read this information sheet.

APPENDIX 1

FEMALE PARTICIPANTS

All female participants will be asked to perform a urinary pregnancy test before the bronchoscopy. This is because the effects of these procedures on a pregnant woman and an unborn baby are not known. This simply involves providing us with a sample of your urine and the test takes 5–10 minutes to perform.

If you are planning to become pregnant during the time of the study, we would recommend that you do not take part. Any woman who becomes pregnant during the course of the study should contact a member of the research team as soon as possible.

What are the implications of undergoing a pregnancy test?

Before you consent to having a pregnancy test, we would like you to take time to consider the implications of taking the test and the result you may receive. A urine pregnancy test is a screening test only and you may require further testing to confirm your pregnancy.

If you test positive and you were planning to be pregnant then this may be good news for you. However, if you were not expecting to test positive, we understand that you might have mixed feelings about being pregnant.

Unplanned pregnancies happen and every woman has the right to decide for herself how to deal with the situation. The result will not be shared with anyone e.g. parent, guardian or GP without your consent.

What support is available in the event of a positive pregnancy test?

Trained staff will be available within the Research Team to discuss, in confidence, the implications of your pregnancy test and direct you to the appropriate sources of further confidential guidance and professional support available through either your local Hospital or your GP. Alternatively The British Pregnancy Advisory Service (BPAS) website www.bpas.org.uk offers valuable information.