

**PARTICIPANT INFORMATION and CONSENT FORM**

**Study Title: 'Randomised placebo-controlled study of grass pollen allergen immunotherapy tablet (AIT) for seasonal rhinitis: time course of nasal, cutaneous and immunological outcomes'**

**Principal Investigator:** Professor Stephen Durham, Head of the Section of Allergy and Clinical Immunology

We would like to invite you to take part in a research study. Before you give your consent, it is important that you read this information. This sheet describes the study. This study will be explained to you and you should also discuss any questions you may have with your doctor and other staff members. You will also be given this information sheet to keep. This should help you decide whether or not you would like to take part in the study. If you sign this consent you agree to take part in this study. You will be given a copy of the signed consent for your records.

**1- Introduction and Background.** About 45 million people in Europe have allergic rhinitis (hay fever) – inflammation of the nasal passages causing sneezing, runny nose, nasal congestion, itching and tearing of the eyes. In the United Kingdom, seasonal hay fever due to grass pollen allergy accounts for approximately 7 times more doctors' appointments than asthma. The standard treatment for hay fever consists of treating the symptoms with a nasal spray and an antihistamine. However, in a survey taken in a UK general practice less than 40% of patients with hay fever reported good symptom control with this standard treatment. For those patients with hay fever whose symptoms are not well controlled by treatment with antihistamines and nasal sprays, subcutaneous immunotherapy (SCIT) - (monthly injections of a grass allergen extract for a period of 3-5 years) is an effective alternative, and is approved in the UK on a named patient basis. More recently, allergen immunotherapy tablets (AITs) have been developed, including grass pollen allergen tablets. These have been shown to be highly effective in the treatment of hay fever, with the additional benefit of being convenient for patients, given that they may be taken at home. Grazax<sup>®</sup> (manufactured by ALK-Abello, Denmark) has UK and EU license for use in the treatment of troublesome grass pollen induced hay fever.

**2- What is the purpose of this research study?** The aim of this research is to investigate the effects of the AIT treatment on the immune system over time – which changes are taking place and when in the course of treatment. This will provide insight into the complexities of the development of allergen-specific immune tolerance – how harmful allergic responses against innocuous substances such as grass pollen can be overridden.

**3- Why have I been chosen?** You have been asked to take part because you have symptoms of hay fever during the grass pollen season - May to July - each summer.

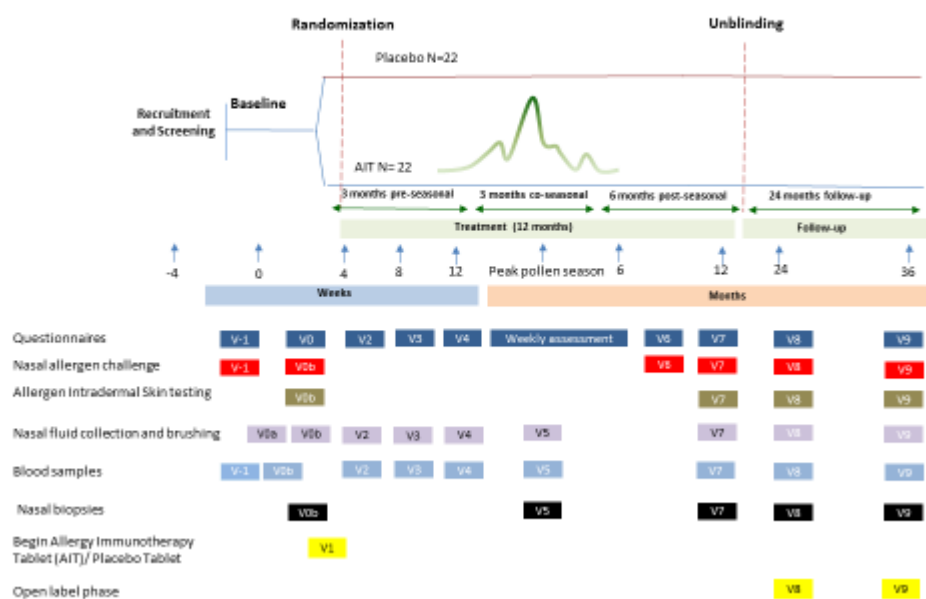
**4- Do I have to take part?** You do not have to take part in this study. Your participation is completely voluntary. If you decide not to take part your future medical care will not be affected in any way. You may also withdraw from the study at any time without having to provide a reason for doing so. You cannot participate in this study if you are pregnant, breastfeeding or if you are planning to become pregnant during the study (see section 15 for more information)

**5- What do I have to do?** You will be asked to come to the Allergy Department at the Royal Brompton Hospital on several occasions over a period of 1-3 years. This will include the following:

- A screening visit (December 2013 – April 2014)
- Two baseline assessments (January – April 2014)
- Randomisation and Treatment (January 2014 - April 2015)
- Five further assessments during treatment (January 2014 –April 2015)

You may then be required (depending on whether you were randomised to receive 'active' or 'placebo' treatment – see below) to continue in the study for another two years. This period will involve continuing to take the immunotherapy tablets for another year, followed by an assessment at the end of that year. After this, no further treatment will be given, but you will be asked to return a further year later for another assessment. If you have been assigned to the placebo group your participation in the study will end after unblinding at 12 months. You will be offered active treatment for 24 months free of charge under regular follow-up.

An overview of the first year of the study is shown in the following diagram; details of what will happen at each visit are given below.



### Screening Visit (V-1)

- Medical history, allergy history, medication record, and allergy skin prick testing
- Physical examination, vital signs (blood pressure, heart rate, weight, height etc)
- Breathing tests (spirometry, peak flow, peak nasal flow)
- Questionnaires concerning hay fever symptoms
- Nasal allergen challenge (grass pollen extract sprayed into the nose)
- Blood sample for full blood count and allergy tests (total 20 ml, equivalent to 2 tablespoons)

- This visit will take approximately 2 – 3 hours

### **Baseline Visits (V0a and V0b)**

During January to April 2014 you will have your first baseline visit (V0a). At this visit you will have the following procedures:

- Vital signs
- Blood sample of 120 ml (8 tablespoons)
- Nasal fluid collection
- Nasal brushing
- This visit will last approximately 60 minutes

During January to April 2014 you will have your second baseline visit (V0b). This visit will be divided into two parts. One will take place in the morning (2 hours), and one in the evening (1 hour), after 8 hours. You will be free to leave the hospital in between. At this visit you will have the following procedures:

Morning visit:

- Vital signs
- Allergen intradermal skin testing
- Nasal fluid collection
- Peak nasal inspiratory flow
- Peak expiratory flow
- Nasal wash
- Nasal allergen challenge

Evening visit:

- Nasal fluid collection
- Nasal brushing
- Nasal biopsy

### **Randomisation and start of treatment (V1)**

In January to April 2014, you will be randomly assigned to receive treatment with either 'active' grass pollen tablets or matched 'placebo' (dummy) tablets. This will be done by a computer programme. Neither you nor the study team will know which treatment group you are assigned to. Following randomisation, you will be asked to attend the clinic to take your first tablet under observation. Before starting treatment you will have your breathing (peak flow rate) and vital signs (blood pressure, heart rate) checked. You will then need to remain in the clinic for 1 hour after taking the first tablet. Both the active and placebo treatments are rapidly dissolving tablets, placed under the tongue. After this, you will be asked to continue to take your assigned tablets once a day, at home, for the following 12 months. (NB: women of childbearing age will have a urine pregnancy test before starting treatment/placebo).

### **Treatment Visits (V2 – V7)**

Over the next 4 months, further visits will be at around 4 weeks, 8 weeks and 12 weeks (V2, V3, V4) after starting treatment. The following procedures will be undertaken:

- Record of current medications

- Record of adverse events
- Vital signs
- Questionnaires
- Blood sample of 120 ml (8 tablespoons)
- Nasal fluid collection
- Nasal wash
- Nasal brushing

These visits will take around 60 minutes each.

At the start of the pollen season, around the 1<sup>st</sup> of May, you will receive a 'rescue medication' pack (nasal spray, anti-histamine tablets, eye drops) for use as required during the season. You will be asked to fill out weekly questionnaires during the season, detailing your symptoms and the amount of rescue medication you have used.

During the peak of the pollen season (mid-June to mid-July 2014) you will be asked to attend the clinic for the following (V5):

- Record of current medications
- Record of adverse events
- Vital signs
- Questionnaires
- Blood sample of 200 ml (16 tablespoons)
- Nasal wash
- Nasal fluid collection
- Nasal brushing
- Nasal biopsy

This visit will take around 2 hours.

At around 6 months treatment, shortly after pollen season, you will be asked to fill out questionnaires concerning your overall hay fever symptoms during whole of the pollen season (V6). Further you will be asked to perform a nasal allergen challenge and you will then be asked to record any hay fever symptoms you have at 5, 15, 30, and 60 minutes after the spray. This visit will take around 90 minutes.

After 12 months treatment (V7), you will be asked to attend for the same series of tests as previously undertaken at V0a and V0b:

Morning visit:

- Vital signs
- Blood take
- Allergen intradermal skin testing
- Nasal fluid collection
- Peak nasal inspiratory flow
- Peak expiratory flow
- Nasal wash
- Nasal allergen challenge

Evening visit:

- Nasal fluid collection

- Nasal brushing
- Nasal biopsy

This visit will take 2 hours in the morning and 1 hour in the evening. You will be free to leave the hospital between these times.

### **Follow up Visits (V8-V9)**

After 12 months unblinding of treatment will take place, meaning you will be told whether you were in the group receiving active or placebo treatment. If you have been on active treatment you will continue treatment for another 12 months, after which time you will be asked to attend for a blood sample of 200 ml (16 tablespoons), nasal brushings, nasal allergen challenge, intradermal skin tests and nasal biopsy (V8). Following this, you will not receive any further treatment, but will be asked to return in another 12 months, for the same procedures to be repeated (V9).

If you were receiving placebo treatment, you will be offered 2 years treatment with active tablets, but will not be required to re-attend for the above procedures. All participants will be contacted periodically by telephone during the 24 months after unblinding to allow reporting of any health problems and current medications.

### **Description of Procedures**

**Nasal Wash (Lavage) (2 minutes)** Nasal lavage with salty water (SinuRinse®) will be used. After ensuring a suitable temperature, the nozzle of the bottle is placed into the volunteer's nose to form a seal, and, with the volunteer leaning forward over a sink, the bottle is then squeezed to allow a jet of solution to pass into one nostril and out of the other. The process is then carried out into the other nostril and repeated several times until all of the solution has been used.

**Nasal Fluid Collection (2-5 minutes)** Small pieces of sponge will be placed into each nostril using sterile forceps for 2-5 minutes in order to collect nasal fluid. They are then removed and the fluid later extracted and frozen.

**Nasal Allergen Challenge (1 hour)** A small amount of purified grass pollen extract will be sprayed into your nose. You will then be asked to record any hay fever symptoms you have at 5, 15, 30, and 60 minutes after the spray. Additionally, we will record how well you can sniff through your nose, using a Peak Nasal Flow meter, how well you can breathe in, using a Peak Flow meter, and will collect nasal fluid.

**Nasal Biopsy (30 minutes – 1 hour)** We shall take 3 nasal biopsies (each ~2mm across) from the lining of your nose at baseline, during the season and at 12 months of treatment. In those participants on active treatment, biopsies will also be taken at 24 and 36 months. Before taking the biopsies we will numb the inside of the nose by applying a local anesthetic by nasal spray and on cotton wool. Biopsies are taken with specialized forceps. The procedure is very well-tolerated and is pain free due to the local anaesthetic. About 10% of patients may experience discomfort following the procedure when the numbness wears off. This discomfort usually responds to paracetamol tablets. Nasal bleeding may also occur in the hours/days after the biopsy. This usually responds to simple finger pressure (pinching the bridge of the nose). It is very rare for any further intervention to be required; nonetheless, a study investigator will be available by telephone 24 hours a day to give further advice should this be required.

**Nasal brushing (5 minutes)** This involves inserting a small brush/probe inside each nostril, before brushing/scraping it against the lining of the nose, it is used to collect cells. This will be performed on seven occasions: twice during baseline, at 4, 8 and

16 weeks, and at 7 and 12 months on treatment.

**Allergy Skin Prick Testing** Skin testing involves putting drops of allergy extracts on the forearm and lightly pricking the skin with a sterile lancet through the allergy extracts. The results are apparent within 15 minutes.

**Allergy intradermal skin testing** This involves injecting a tiny amount of grass allergen solution just under the skin of the forearm. After 15 minutes a small skin wheal will be apparent in allergic individuals and is recorded with a pen. After 8 hours, a larger, more diffuse swelling becomes apparent – this is recorded with a pencil at 8 hours.

**Lung Function Testing** This involves breathing through a tube into a machine to measure how well your lungs are working.

**Research Tests** Blood and biopsy samples are collected during the study. These samples are used for research tests. Research tests help us learn more about your disease, the immune system (the body's natural defense system against illness), and response to drugs or treatment. The results of the research tests will not be shared with you. These research samples will not identify you. Research tests may include genetic tests. Genetic tests study an individual's inherited characteristics, found in DNA, which is present in each of the cells of your body. DNA contains information needed to construct and operate a human body.

## **6- What is the drug or intervention that is being tested?**

Grazax® Standardized Grass Pollen Tablets contain purified grass pollen extract in a fast dissolving pill form taken under the tongue.

Grazax® contains gelatine (fish source).

## **7- What are the possible effects of the procedures and interventions being tested?**

### **Study Medication Risks**

**Grazax® Standardized Grass Allergy Tablet.** Very commonly reported side effects (occurring in up to 70% of patients) include itching and mild discomfort within the mouth. In a few cases, this may develop into tongue and/or lip swelling, or mild blistering in the mouth. Other common side effects of Grazax® include headache, fatigue, red, itchy, watery eyes, sneezing, nasal congestion, itchy nose, runny nose, irritation and swelling of the roof of the mouth, itchy ears, mild asthma (wheezing, cough), itchy skin rash and hives. Abdominal symptoms may include stomach irritation, acid reflux, vomiting and diarrhoea. These side effects are mostly mild to moderate in severity, last from minutes to hours after each intake of Grazax®, and tend to go away on their own within 1 to 7 days. These side effects are usually well-tolerated and require no treatment. However, anti-allergic medication is always available.

More severe, systemic allergic reactions, including anaphylaxis, to Grazax have been reported, but they are exceptionally rare, occurring at a frequency of less than once per million tablets taken. None the less, in view of the potential risks involved, the first tablet is taken under medical supervision over 60 minutes and there is a 24-hour telephone contact line for advice concerning any side effects at any time.

The usual medication information sheets for Grazax® are available on request.

## **Study Procedure Risks**

**Intradermal and Skin Prick Tests** These tests are routinely performed in clinic. You may experience mild to moderate itchiness and discomfort at the sites of the intradermal and skin pricks with allergens and the positive control (histamine). The symptoms are usually not bothersome and treatment with topical or oral antihistamines is available if needed. In view of the extremely remote risk of a more serious reaction a physician is always present and drugs and equipment for treatment of anaphylactic reactions are available.

**Nasal Allergen Challenge** You will experience typical hay fever symptoms including nasal itching, nasal blockage, sneezing, nasal discharge, itchy eyes, watery eyes, and redness of the lining of the eye. Nose and/or eye symptoms are prominent within minutes and fade rapidly, whereas mild nasal congestion may last up to and after 10 hours. There is a small risk of causing mild asthma symptoms. You will perform a breathing test (using a "Peak expiratory flow meter") before and after the nasal challenge and treatment with inhaled bronchodilators and steroids will be immediately available. As discussed above, for any intervention using the allergen to which you are allergic, there is that small risk of developing an anaphylactic reaction, although this has never been observed in studies of several hundred participants over the past 20 years in our department.

**Nasal Wash (Lavage)** Nasal wash with salty water (SinuRinse®) will be used before and after the nasal challenge. SinuRinse® is widely available and no adverse effects are to be expected.

**Blood Samples** You will feel the sting of the needle as it enters a vein in your arm. There is a small risk of bruising and swelling at the site where the needle is inserted. Some people feel faint when they have their blood taken. You will be seated when you have your blood sample taken. True faints ('vaso-vagal' faints) are rare and resolve on lying down.

**Nasal Brushing** This may provoke discomfort and very rarely mild nasal bleeding. Local anaesthetic spray may be applied before the procedure if preferred.

**Nasal Biopsy** The most frequent side effects are local discomfort, which may persist for up to 5-7 days, and nose bleeding. This occurs in about 1 in 10 biopsies taken in our centre and responds to conservative measures including application of finger pressure below the nasal bridge. In order to minimize discomfort, the inside of the nose is pre-treated with a highly effective local anesthetic (numbing medication) given by a spray pump directly onto the inner lining of the nose. In order to provide complete numbness and to minimize the risk of bleeding, cotton wool soaked in a numbing solution is applied to the inner lining of the nose for 10 minutes before the procedure. There may be a slightly bitter taste from either the solution or the local spray used.

The treatment and procedures in this research study may have risks that are not yet known.

**8- Who will benefit from the study?** Taking part in this trial may or may not be of benefit to you. However, your participation in the study may benefit society by helping us learn more about better ways to treat allergies in the future. During the pollen season you will be provided with medications to alleviate your symptoms in the nose and eyes. This "rescue medication" set will include antihistamine tablets, nasal corticosteroid sprays and eye drops. Further you will receive 24 months of active treatment free of charge either from the beginning of the treatment if you were

assigned to the active treatment group or after unblinding at 12 months if assigned to the placebo arm. We believe this active treatment to have a positive effect on your hay fever symptoms during the pollen season.

**9- What other choices do I have if I do not take part in this study?** Before you decide to take part in this study, Prof. Durham or his medical colleagues will talk with you about these and other options you may have, which may include just staying on the standard treatment for your hay fever.

**10. May I leave this study at any time?** You may decide not to take part or to withdraw from the study at any time. If you decide to withdraw from the study, there is no penalty or loss of benefits in your routine medical care or any other benefit(s) that you would otherwise be entitled to receive.

If you or the study doctor decides that you should stop taking the study medication, we would like to have you continue with the study visits and procedures, so as to follow your progress after coming off the study medication. This will also be very helpful for comparison to those participants who continue on the study medication for the duration of the study.

In addition, you should consult with Prof. Durham who will discuss future treatment and procedures for your continued care when you are no longer in this study.

**11- Can I be taken off this study without my consent?** You may be removed from the study without your consent at any time. Reasons why you may be removed from the study include, but are not limited to, the following:

- Prof. Durham decides that it is best for you not to continue.
- You are unable to complete study treatments or tests.
- The study is stopped by the Institution, the Sponsor(s), or the Medicines and Healthcare products regulatory agency (MHRA), or other Health Authorities.
- You meet one of the pre-defined stopping rules as written in the study protocol.

If you are removed from the study Prof. Durham will notify you about treatment or procedures for your continued care.

**12. What about new findings?** During your participation in this study, Prof. Durham will also discuss with you about any new findings so you are up-to-date and to allow you to decide whether such findings from this or other research may affect your willingness to continue in the study.

**13- What if something goes wrong?** It is important that you tell your study doctor, Prof. Stephen Durham, Dr. Moisés Calderón or Dr. Esther Steveling if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call Prof. Stephen Durham on 020 7351 8024, Dr. Moisés Calderón or one of the other study doctors (Dr Esther Steveling) at the Royal Brompton & Harefield NHS Foundation Trust. A 24hour telephone contact number 07714 051 248 will be available at all times during the study.

For further support, assistance and advice the Royal Brompton Hospital offers the Patient Advice and Liaison Service (PALS). They can help you if you are having difficulties, or any complains. You may contact: Patient Advice and Liaison Services (PALS), Royal Brompton Hospital, Sydney Street, London, SW3 6NP, Tel: 020 7349 7715, Email: [pals@rbht.nhs.uk](mailto:pals@rbht.nhs.uk).

**14- Will my taking part in this study be kept confidential?** Your medical and research records will be confidential to the extent permitted by law. Every effort is



made to keep your identity private. You will be identified by a study code, not your name. All of your results from the study, including blood and nasal samples, will be collected and stored under this number, rather than using your name or other personal identifiers. The key to the code is kept in a secured file at the study site.

All of your results and samples will be stored securely on-site at Imperial College. Blood and nasal samples will be analysed at Imperial College, London, at King's College, London, and at ALK Abello, Horsholm, Denmark using only the study code number. Only the investigators directly involved in running the study will have access to these results. Only the study staff at the Royal Brompton Hospital will have access to your personal identifiable information; other investigators, in particular those investigators analysing your blood and nasal samples, will only be able to identify you by your study code number. Authorised personnel from Imperial College, Royal Brompton Hospital NHS R&D offices and regulatory authorities/inspectors may need to access to your clinical notes if they need to verify or cross-check data.

**15- What about pregnancy, breastfeeding and birth control?** You cannot participate in this study if:

- You are pregnant
- You are planning to become pregnant while in the study or
- You are breastfeeding

Initiation of treatment with Grazax is not recommended during pregnancy. Additional procedures undertaken in this study are also not recommended in pregnancy. If you are female, you will be given a pregnancy test before the study. If you join this study, you must agree to use birth control during the entire length of the study. If you should become pregnant while in this study, or if you think that you have become pregnant, you must contact one of the investigators right away.

**16- Will my GP be informed?** With your consent we will inform your GP about your participation in this study.

**17- Ethics Approval** This study has been reviewed and approved by the Research Ethics Committee East Midlands – Nottingham 2.

**18- What will happen to my samples?** Blood and nasal tissue samples will be stored and analysed in the laboratories at Imperial College, King's College, and ALK Abello, (Horsholm, Denmark). The response of certain cells within the samples, including numbers of different cell types, mediators released and genes switched on or off, will be studied.

**19 - Will my blood, and/or tissue samples and information from this study be stored for future research use?** With your consent any specimens left over at the end of the study will be stored securely under your coded number for up to 10 years at Imperial College, London, and will be used for future ethically approved research.

Samples will not be analysed or tested for serious infections, such as HIV or Hepatitis B, nor for any inherited genetic conditions.

The results of tests done on your stored samples will not be given to you or your doctor. The results will not be put in your records and will not change your medical care. There will be no benefits to you from the storage of these samples and information. However, the use of your samples and information may help researchers learn more about your disease or help study the genetics related to your disease.

There may be risks in allowing the storage or analysis of samples and information. Researchers are required to protect your privacy and to keep your information private to the extent permitted by the law.

Future studies on stored samples and information will be reviewed and approved by an Ethics Committee for science and ethics. The samples and information will not be sold; however, the results of the tests could lead to the development of commercial products. You will not receive any money from research using your stored samples and information.

You can change your mind at any time during the study and ask to have your samples destroyed. This request should be made in writing to the study doctor. If your samples have not been used, they will be destroyed. If your samples have already been tested before your request, the information from these tests will be used and cannot be destroyed.

**20- What will happen to the results of the research study?** The results of this study will help us to improve our knowledge about hay fever and allergy. We are not seeking financial benefits from this study.

**21- Who is organising and funding the research?** None of the study investigators have any personal financial interest in the study. This study is being conducted by Imperial College London.

**22 - What if I have a problem or a question?** If you ever have questions about this study or have a study-related injury, you should contact Prof. Stephen Durham, Dr. Moisés Calderón (or another study doctor) on 020 7351 8024 or 07714 051 248 (24 hours) at the Royal Brompton & Harefield NHS Foundation Trust.

For further support, assistance and advice the Royal Brompton Hospital offers the Patient Advice and Liaison Service (PALS). They can help you if you are having difficulties, or any complains. You may contact: Patient Advice and Liaison Services (PALS), Royal Brompton Hospital, Sydney Street, London, SW3 6NP, Tel: 020 7349 7715, Email: [pals@rbht.nhs.uk](mailto:pals@rbht.nhs.uk).

**23 - What are the costs of taking part in this study?** Taking part in this trial will not cost you anything. You will be reimbursed any reasonable travel and parking expenses incurred throughout your participation in this clinical study upon providing receipts.

**24 - Will I be paid for taking part in this study?** You will receive no payment for your participation in this research study, whereas you will receive £75 compensation for each visit. Please be advised, that receiving a payment to take part in the study may affect any benefits that you claim.

To be printed on departmental headed paper

Study Protocol Number: 13IC0847 V 7.0

Study Participant ID: \_\_\_\_\_

### CONSENT FORM

**Full Title of Project:** A Prospective Randomised Placebo-Controlled Time Course Study Of Grass Pollen Allergen Immunotherapy Tablet (AIT) Treatment For Allergic Rhinitis: Study of nasal, cutaneous and immunological outcomes.

**Name of Principal Investigator:** Professor Stephen Durham

**If you agree,  
Please initial box**

1. I confirm that I have read and understood the subject information sheet dated 01.10.2015 version 6.0 for the above study and I have had the opportunity to ask questions which have been answered fully.
2. I understand that my participation is voluntary and 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 sections of any of my medical notes may be looked at by individuals from Imperial College, Royal Brompton & Harefield NHS Foundation Trust and other regulatory authorities I give permission for these individuals to access my records that are relevant to this research.
4. The compensation arrangements have been discussed with me.
5. I agree to take part in the above study.
6. I consent to my blood and tissue samples being used for laboratory research tests as described in the protocol.
7. I agree to my samples to be stored and used in future, REC approved projects.
8. I consent to my GP being informed of my participation in the study.

\_\_\_\_\_  
Name of Subject

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date

\_\_\_\_\_  
Name of Person taking consent

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date

1 copy for subject; 1 copy for Principal Investigator; 1 copy to be kept with hospital notes