**Deciphering the Mechanisms of Pain in Paget’s Disease**

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| **Introduction to the PIP study.** |
| We would like to invite you to take part in a research study concerning the mechanisms of pain in Paget’s disease called the Pain in Paget’s disease study (PIP study) Before you decide whether or not to take part it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Once you have read the form. Please feel free to ask the doctor or the nurse involved in the study about anything that is not clear or if you would like more information. You can take as much time as you need to decide whether or not you wish to take part. |
| **What is the purpose of the study?** |
| Our main aim is to gain greater understanding of the causes of pain in Paget’s disease. Many patients with Paget’s disease experience pain, but we are still not entirely sure what the causes are, nor why some people with high levels of activity of Paget’s disease experience no pain, while others experience severe pain. We believe that there are a number of factors in play and we want to investigate these in detail. This would involve asking you about your symptoms and taking blood samples to check biomarkers of disease activity. We will also look at your DNA to see whether there are any genetic factors associated with your pain levels. Even if you do not experience any bone pain, you will still be an important part of this study, because we can learn a lot by comparing the characteristics of people who have pain with those who do not.  |
| **Why have I been invited to take part?** |
| We have invited you to participate in this study because you have been diagnosed with Paget’s disease.  |
| **Do I have to take part?** |
| No, it is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be invited to sign the consent form that is at the end of this information sheet. If you decide to take part you are still free to withdraw at any time and without giving a reason. Deciding not to take part or withdrawing from the study will not affect the healthcare that you receive, or your legal rights.  |
| **What will happen if I do take part?** |
| If you agree to take part in the study, we will ask you to do the following: * Provide a blood sample for analysis. In most cases, this will be about 20ml (or 4 teaspoons) and will normally be collected at the same time as your usual blood tests when you come up to the clinic.
* To provide stool and saliva samples for analysis. We will provide special kits for this. You can collect them at home and either bring them into the clinic on the day of appointment or send them directly by post to the trial co-ordinating centre
* Complete some questionnaires about your pain and your quality of life. If you need help filling them in (for example, if you have poor eyesight, or difficulty holding pen) one of the research staff will be happy to assist you
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| * Complete a questionnaire regarding your diet and your physical activity levels. It’s known that both diet and exercise can influence the microbiome which we think might play a role in PDB
* Have what is called ‘Quantitative Sensory Testing’, or QST. These are a series of short tests which can be done at the clinic which will help us understand the mechanisms of your pain by assessing how you perceive sensations, including temperature, vibration, and pressure:
	+ **Hot/Cold:**  We will look at how you perceive temperature using warm and cold rollers.
	+ **Vibration:** A tuning fork will be placed lightly on your skin. There will be brief changes in vibration and we will ask you to tell us if/when you feel anything.
	+ **Pressure:** We will use a set of filaments called von Frey hairs to assess your response to varying degrees of pressure. Each ‘hair’ will be pressed against the skin and you will be asked to tell us when you can feel the pressure. We will also do a test called a pinprick test (with a small pin) to measure your response to pain.

The only discomfort you might experience with these tests is with the pinprick test when we touch your skin with a small pin. Any pain experienced as the result of this test is mild and only lasts for a moment.Whenever possible we will perform all the tests and questionnaires on a single day which we will try and co-ordinate with one of your normal clinic visits.  |
| **Are there any follow up visits?** |
| Not usually. In most people the study involves only a single visit. However, if your doctor decides that you have pain that might be caused by PDB and thinks that treatment is advisable then we will ask you to undergo some of the tests again to see how that treatment has affected your perception of pain. When patients have treatment for PDB, its normal practice for a follow up visit to be organised to determine how well the treatment has worked and for repeat blood tests to be performed. If a repeat clinic visit is organised by your doctor we will organise for the follow up assessments to be done at the time of that visit.  |
| **What will happen with the samples you collect?**  |
| One of the blood samples will be used for analysis of your genetic make up to see if this has an influence on pain or severity of your Paget’s disease. Another will be used to measure biochemical markers of bone metabolism, including the level of alkaline phosphatase, which are sometimes raised in people who have Paget’s disease. The stool and saliva samples will be used to analyse makeup of bacteria and other microorganisms in your gut and mouth. Everyone carries many millions of non-harmful bacteria and other microorganisms at these sites and we want to determine if the profile of these organisms differs in people with PDB as opposed with those that do not have PDB, as well as to evaluate if they influence pain.  |
| **Will you be keeping these samples after the study has finished?**  |
| Yes. We want to keep the samples for up to fifteen years after the study has finished. The reason for this is that they may be valuable for future research into Paget’s disease and other bone diseases. Although several tests are available at present to assess people with Paget’s disease, none of them are perfect and it’s possible that in the future, new tests may be developed for the diagnosis or monitoring of Paget’s disease. If you allow us to keep your samples they may be used in future research studies into Paget’s disease, provided that these studies have been ethically approved. Please be assured that if we do use your samples in future studies your personal details will not be shared with researchers that might wish to analyse the samples. |
| **Will any genetic research be performed?** |
| Yes. The study will involve taking samples for genetic analysis. One of the genes we will analysis is called *SQSTM1*. We already know that people who have particular variants of *SQSTM1* are more susceptible to PDB and that these variants can be passed onto 50% of their children who also would be at increased risk of developing PDB. We would be in a position to let you know if your sample tests positive for *SQSTM1* once the sample has been analysed. If you wish to be informed of that result please can you let a member of the research staff know at the study site and also initial the relevant box on the consent form. If you want to know the result of this test a member of the research team will be able to explain what it means for you and your family.  |
| **Is there anything I need to do or avoid?** |
| No. Participation in the study doesn’t involve any particular preparation on your part |
| **What are the possible benefits of taking part?** |
| The aim of the study is to gain better understanding of the causes of pain in PDB. This could help future generations of people with PDB by gaining greater understanding of the causes of pain which in turn could lead to more effective treatment.  |
| **What are the possible disadvantages of taking part?** |
| If you take part in the study it will usually involve extending your clinic visit which may take up to an hour longer than usual depending on whether you complete the questionnaires at home or at the clinic. You may experience mild discomfort for a moment when you have the pinprick test for the sensory testing and when you have a blood sample taken. Having the blood test can also result in local bruising. In order to minimise discomfort, we will endeavour to take the extra samples of blood for the research study at the same time as your routine blood samples in which case there would be no additional discomfort. |
| **What if there are any problems?** |
| If you have a concern about any aspect of this study please contact Professor Stuart H Ralston, the chief investigator by telephone on 0131-651-8741 or by email stuart.ralston@ed.ac.uk. Professor Ralston will do his best to answer your questions. If something goes wrong and you are harmed during the research and this is due to someone’s negligence then you may have grounds for a legal action for compensation but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you (if appropriate). |
| **What will happen if I don’t want to carry on with the study** |
| You are free to withdraw from the study at any time. If you decide to withdraw you don’t have to give us a reason why, and your decision to withdraw will not affect the standard of medical care that you receive. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible. You will have the option to decide whether or not you would like to hear from us again with regard to the results of the study or other research into PDB. If you do decide to withdraw, a member of the research team will find out which option you would prefer.  |
| **When will the study finish?** |
| The study will finish when we have recruited the target number of patients from across the UK and when everyone has completed the assessments. From your point of view as a participant, the study will finish after you have completed the assessments described in this information sheet. This will usually be done in a single day but of you are undergoing treatment for PDB and coming back for another clinic appointment we may ask you to repeat some of the assessments. There is no long-term commitment beyond that but we will ask your permission to be able to contact you about ethically approved studies on PDB that might be performed in the future so see if you are interested in those.  |
| **What happens when the study is finished?** |
| Following completion of the study we would like to keep the samples and data we have collected about you for up to 15 years. There are two reasons for this. The first is that technically the study is considered to be finished when we recruit the last patient and would be almost impossible for us to conduct all the analyses we need to perform on the same day as the last patient is recruited. The research we are performing is technically demanding and might take 1 year or even 2 years to complete. Even after we have finished the analysis we would like to keep the samples that you have donated on a long term basis. The reason for this is that the samples and data may be extremely valuable for future researchers who are studying PDB. An example would be if a new test to predict pain PDB was developed in 5 or 10 years’ time we would be able to use the samples we have obtained from you that are in storage to investigate how good that test is. This could benefit future generations of people with Paget’s disease. We also would like to be able to access your health records after the study has finished and we will ask you to consent to this. The reason for this is that PDB is a chronic condition that people live with for many years. The research we are performing will give an insight into the mechanisms of pain at a single time point but it would be very valuable to see if the information we collect now may be of value in predicting future complications of the disease like arthritis or fractures. If we have your permission to use record linkage to determine if you develop complications of PDB in the future this could be tremendously valuable for future generations of people with PDBWe can do this through organisations such as the Information Services Division (Scotland), the NHS Central Register, NHS digital and other NHS organisations that hold data. This will allow us to enquire about your long-term health status and collect additional information relevant to the study through ‘record linkage’ which is the name given to the procedures when medical information from two or more sources are brought together. It would not involve any additional study visits. We will also ask your permission to contact you directly about future research studies into PDB and to contact your GP or other healthcare provider about your health status.  |
| **Will my taking part be kept confidential?** |
| Yes. All the information we collect during the course of the research will be kept confidential and there are strict laws which safeguard your privacy at every stage. We will ask you to consent to us holding personal data so that members of the study team can contact you about the visits. We will also hold a copy of your consent form at the central office. We will ask your permission to keep a record of your CHI or NHS number. These are unique number which are allocated to you and can be used to provide linkage between documents and notes pertaining to your health and treatment. We will also seek your permission to access your medical records as part of the PiP study. In order to monitor and audit the study we will ask your consent for responsible representatives from the sponsor(s) and NHS Institution(s) to access your medical records and data collected during the study, where it is relevant to you taking part in this research. The Sponsor(s) is/are responsible for overall management of the study and providing insurance and indemnity.We will inform your GP that you are taking part in the study provided that you consent to us doing so. All the information we collect during the course of the research will be kept confidential and there are strict laws which safeguard your privacy at every stage. |
| **Why do you need my personal information and how will you use it?** |
| We need to have information from you and/or your medical records in order to undertake this study. The reason that we need to store this information is so that we can perform the research that is described in this information leaflet. The University of Edinburgh and NHS Lothian are co-sponsors of the study and will act as what is called the data controller for this study. The data controller is responsible for looking after your information and using it properly. The data we collect about you will be kept by storage on secure computer systems at the University of Edinburgh. Access to your data will be restricted to members of the study team on secure computer systems which will be protected by usernames and passwords. In order to maximise security, we will ensure that any personal data we hold about you is in a different location to other study data which will contain the results of your blood tests and questionnaires. Any paper records we hold about you such as consent forms will be stored in locked cabinets within secure buildings to which only members of the study team have access. We may share anonymous data from the study with other doctors and scientists or commercial organisations who are conducting research on Paget’s disease and other diseases in the UK, Europe and other countries. If we do this, we will only share what’s called “anonymised” data. This means that any data that is shared would not include any personal details and could not be used to identify you. The principal investigator of the study, Professor Stuart H Ralston will be responsible for ensuring that your data is held securely.  |
| **Who is organising and funding the research?** |
| The research is being carried out by the University of Edinburgh and is funded by the Paget’s Association. Some members of staff involve in the study are also supported by a grant from the European Commission. It is possible that commercial organisations such as pharmaceutical companies and other academic researchers in the UK or overseas might collaborate in this study, assist us with aspects of the analysis or provide financial support to assist with the research. In return, these organisations might request commercial rights to discoveries that occur as the result of their funding. To allow such collaborations to proceed you are asked to waive any future claim to financial benefit through participation in the study. The sample you donate is treated as a gift and remains in the custody of The University of Edinburgh. In this respect we should point out that it is the whole collection of many thousands of samples that is of value and that each individual sample has in reality no commercial value on its own. Whatever happens in terms of commercial development it is our intention that: 1. Any significant discoveries or inventions will be patented where possible, both to maximize the value of the research and to provide incentives for companies to develop the new therapies;
2. A proportion of the revenues from any commercial involvement will be channelled back into research into bone and joint disease at the hospitals and universities that participate in the study.
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| **Who has reviewed the study?** |
| The study has also been reviewed by members of the Paget’s Association, a patient support organisation. All research in the NHS is looked at by an independent group of people called a Research Ethics Committee. A favourable ethical opinion has been obtained from the West of Scotland Research Ethics Committee 03. NHS management approval has also been given. |
| **Researcher Contact Details** |
| If you have any further questions about the study please contact Professor Stuart H Ralston by telephoning 0131-651-8741 or by emailing: stuart.ralston@ed.ac.uk. You may also write to Professor Ralston: The Centre for Genomic and Experimental Medicine, MRC Institute of Genetics and Molecular Medicine, Western General Hospital, Edinburgh, EH4 2XU.  |
| **Independent Contact Details** |
| If you would like to discuss this study with someone independent of the study please contact Dr Adrian Tan by emailing: adrian.tan@nhsborders.scot.nhs.uk. You may also write to Dr Tan at: Rheumatology Department, Borders General Hospital, Melrose, TD6 9BS.If you would like general advice about participating in research you can get in touch with: [Please insert the details of the relevant Patient Advice Service (i.e. PASS in Scotland, PALS in England)] |
| **Complaints** |
| If you wish to make a complaint about the running of the study please contact:[Please insert the details of the relevant local complaints office] |

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|  | Please **initial** box |
|  | 1. I confirm that I have read and understand the information sheet (05/04/2019, Version 4) for the above study. I have had the opportunity to consider the information, ask questions and have had these questions answered satisfactorily.
 | ⬜ |
|  | 1. I understand that my participation is voluntary and that I am free to withdraw at any time without giving a reason and without my medical care and/or legal rights being affected.
 | ⬜ |
|  | 1. I give permission for the research team to access my medical records for the purposes of this research study
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|  | 1. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the Sponsor (University of Edinburgh and/or NHS Lothian), from the NHS organisation or other regulatory authorities where it is relevant to my taking part in this research. I give permission for these individuals to have access to my data and/or medical records.
 | ⬜ |
|  | 1. I give permission for my personal information and a copy of the consent form to be held by the study team for administrative purposes
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|  | 1. I give permission for my Community Health Index (CHI) number or NHS number to be held by members of the study team at University of Edinburgh so that they can track any complications of PDB that may occur in the longer term through record linkage.
 | ⬜ |
|  | 1. I give permission for the anonymised data and samples collected during the study to be stored at the University of Edinburgh for use in this study and future ethically approved research studies into Paget’s disease and related diseases
 | ⬜ |
|  | 1. I agree to give blood samples for genetic (DNA) testing and analysis of gene expression **and give permission for whole genome or exome sequencing** to be conducted on this sample
 | ⬜ |
|  | 1. I want / do not want (delete which is applicable) to be informed about the result of genetic testing for SQSTM1 gene variants.
 | ⬜ |
|  | 1. I agree to my GP being informed of my participation in the study
 | ⬜ |
|  | 1. I agree to being contacted about future ethically approved studies in PDB.
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|  | 1. I agree to take part in the PIP study
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Name of patient Date Signature

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Name of person taking consent Date Signature

1x original – into Site File; 1x copy – to Participant; 1x copy – into medical record