Principal Investigator: Prof Katy Vincent
Nuffield Department of Women's and Reproductive Health
University of Oxford
katy.vincent@wrh.ox.ac.uk

PARTICIPANT INFORMATION SHEET

For participants 16 and over

RoADPain: Understanding the Importance of Period Pain in Teenagers

We would like to invite you to take part in our research study. Before you decide, it is important that you understand why the research is being done and what it would involve for you. There is no direct benefit to you for taking part, although you will be reimbursed for your time. Please take time to read this information, and discuss it with others, such as your parents, if you wish. *If there is anything that is not clear, or if you would like more information, please ask us.*

What is the purpose of the study?

Chronic pain is defined as pain that lasts for more than 3 months. It is really common, affecting up to 30% of people worldwide with impacts on all areas of life. Chronic pain is difficult to treat once it has developed. Therefore, understanding which people might be at risk of developing chronic pain and protecting them from it starting, would be a really positive step forward.
We know that women are more likely to develop almost all types of chronic pain than men. We start to see this sex difference in chronic pain after puberty, suggesting that changes happening at this time may be contributing to this increased risk. One important change that happens at this time is periods starting. Despite periods often being very painful, period pain has traditionally been dismissed as "normal" and something girls must learn to live with.
However, in adult women with period pain we see many differences across a range of body systems when compared to women without period pain. The aim of this study is to look at these body systems in young people who menstruate in the first few years of having periods. To do this we will use a combination of questionnaires, brain scans and tests of body systems (including nerve function (how things are felt on the skin), stress response and bladder sensitivity). We hope that this work will reduce the risk of both young people and adults suffering with period pain and other chronic pain conditions.

Why have I been invited?

You have been invited to take part in this study as you are:

- You are aged 11-20

- You have had at least 6 periods a year since your periods started
- You have not used hormonal therapies (such as the pill or the mini-pill) in the past for any reason.

We hope that around 120 people will take part in this study. People who have had periods for between 1 and 6 years, with or without experiencing period pain.

Do I have to take part?

No. It is up to you.
If you do decide to take part please call or email us; our contact details are provided at the end of this information sheet. If you decide to take part, we will ask for your consent and then ask if you would sign a form. We will give you a copy of this information sheet and your signed form to keep. You are free to stop taking part at any time during research without giving a reason. If you decide to stop, this will not affect any care you receive now or in the future.
If you decide not to take part, you do not need to do anything and it will not affect any care you receive now or in the future.

What will happen to me if I decide to take part?

There are 4 main parts to this study and we ask you to take part in them all:

1) Questionnaires
2) Saliva (spit) collection
3) Testing of pain-relevant systems
4) Brain scan (fMRI) if you are happy to do this and the researchers agree that it is safe for you.

We will describe what happens in each part of the study separately. We will ask you to complete the questionnaire at the start of the study. The testing of pain-relevant systems and the brain scan (if appropriate) we will do twice, at different times of your menstrual cycle (once during your period and once around 10 days after a period).

For any/all study visits you are welcome to bring a parent or friend along with you, although they may not be able to be in the room with you for all aspects (such as during the brain scan).

1) Questionnaires

When you first start the study, we will ask to you to fill out a questionnaire about various aspects of your life, including information about your periods and your wellbeing. We expect this will take about 15 minutes to complete.

At each visit we will also ask you to fill out a short “How are you today?” questionnaire about how you are feeling.

We will also ask you to complete another questionnaire at the end of the study, depending on our study results.

2) Saliva (spit) collection

We will ask you to collect saliva during your study visits and at home. For these we will ask you to chew something and spit into a tube. We will explain how to do these during a visit. We will give you paper instructions for any you collect at home. In total we will ask you to collect 14 samples. One of your saliva samples will be used to look at genetics, there is more information about this in the section ‘What will happen to the samples I give?’.

3) Testing of pain relevant systems

The second part of the study will involve you coming in to the John Radcliffe Hospital at two different times. The timings of these will be around your menstrual cycle, with one session during your period and the other around 10 days after a period. These visits will take about 4 hours each, plus any break times. If you have brought someone with you, they can be in the room whilst we explain what we will be doing but we will ask them to step outside the room for the tests. This is because having someone else inside the room can affect the results of the tests. Ideally we would like you to not drink caffeine or take painkillers on the day of the tests, but it is okay if this is not possible. At the start of the visits, you will complete a short questionnaire about how you feel today.

On our website you can find a video recording of these visits so you can see what these will be like (www.wrh.ox.ac.uk/research/roadpain).

The visits will then include the following parts:

Part 1 is about nerve and muscle function and will last about 1 hour. We will start by testing the function of nerves in response to a variety of different sensations, such as temperature and touch. This is known as quantitative sensory testing (QST). We will use a set of different devices to produce sensations of temperature change, pressure, vibration, and touch on your non-dominant hand (if you are right-handed we will test on your left hand). For each sensation we will ask you to report what you felt. We will also test how you experience different sounds.

Part 2 assesses other systems that can alter pain including your brain's ability to damp down painful sensations, your stress response and the function of your autonomic nervous system, which controls how fast your heart beats and your blood pressure. This part will last about 1 hour. Firstly, we will also ask for a saliva sample to measure your stress hormones. Then, we will stick pads to the top of your chest to take a tracing of your heart (an ECG) and put a blood pressure cuff around your arm. These will give us all the information we need about your autonomic nervous system. We will then ask you to sit quietly on a seat for about 20 minutes whilst we collect these readings. Next, we will test how you respond to some painful sensations. These will be short and will not cause you any damage. Some sensations will be given on their own, but we will also deliver some quickly after each other to see how they feel to you. Once we have finished these tests we will ask you for another saliva sample and will take a further 20 minute recording of the autonomic nervous system measures.

Part 3 looks at how sensitive your bladder is. This will take up to two hours. About an hour before the test we will ask you to drink plenty of fluid to ensure you are well hydrated. When we start, we will ask you to go for a wee and we can then start the test. You will need to sit quietly in a room for the duration of this visit, but we will give you some puzzles to occupy you. We will give you a fixed amount of water to drink and then, at regular intervals, ask you to rate sensations from your bladder. When you feel your bladder is at its maximum fullness and you can't hold it any longer, we will ask you to go to the toilet and wee in a bowl. Then we will measure the volume. We will stop this part after two hours and ask you go to the toilet then if you haven't already. This may be a bit uncomfortable if it puts pressure on your bladder but should not be painful.

On our website you can find a video recording of these visits so you can see what these will be like (www.wrh.ox.ac.uk/research/roadpain), if you have any questions you can also contact the study team. At the end of the visit, we will give you 5 small bottles that we would like you to collect saliva in the day before your next visit. We will give you instructions about how to collect these samples. We ask you to return these to us at the start of the next visit and we will put them in the fridge.

4) Brain scan fMRI (You may not be eligible for the brain scan for this study (for example if you have a fixed dental brace or claustrophobia), but you may be invited to participate in the other study procedures)

The third part of the study will involve you coming in to the John Radcliffe Hospital at two different times for a brain scan. The timings of these will be around your menstrual cycle, with one brain scan during your period and the other around 10 days after a period. If you have brought someone with you they will not be able to be in the scanner with you, although if necessary they may be allowed into the scan room, depending on safety procedures.

The overall experience of the pain that you perceive is generated by your brain. Functional MRI scans (fMRI) measure brain activity and can assess how your brain processes the pain you may be experiencing at the time and during the experience of other stimuli. The scan will last approximately 1 hour. You will be able to stop the scan at any point if there is anything you are unhappy about and we will talk to you in between each section. Whilst the scan is running we will ask you to lie as still as possible. For the last part of the scan we will look at how your brain responds to stimuli. To do this we use a blunt pin-prick on your lower leg whilst the scan is running, as we have used on your hand in part 2. Most people, even those with pelvic pain, don't find this particularly painful and we will ask you to tell us how painful it is during the scan. At the end of the scan we will take a saliva sample to measure your hormone levels, as we know that hormones can influence how your brain responds to pain. Overall, this visit will last about 1.5 hours. More information about fMRI including how it works can be found on our website (www.wrh.ox.ac.uk/research/roadpain).

This is a photo of the scanner we will be using.

What should I consider?

We are approaching you about this study as we think you meet our criteria, however, there may be reasons why this is not the case.

- If you are taking or have taken hormonal therapies (such as the pill or mini-pill) you will not be able to participate as these will affect your hormone levels and can alter your menstrual cycle.
- If you have or have had in the past, any chronic pain condition (other than period pain), including migraines, you will not be able to participate as it might alter some of the measures we are collecting.
- If you have had a diagnosis of cancer, you will not be able to participate as it might alter some of the measures we are collecting.
- If you are pregnant or breast-feeding then you will not be able to participate as these both affect pelvic pain and also many of the measures we are collecting.
- There are additional specific reasons that may mean that you cannot take part in this study, but we will discuss these with you if you want to take part.

You can tell the researcher if any of these apply to you or you think they might, and we will keep it confidential.

Are there any possible disadvantages or risks from taking part?

We have designed the study with the input of patient and public involvement and engagement representatives, however, there are still some disadvantages associated with being involved:

Time: the questionnaires will take time to complete and may seem repetitive or not relevant to you.

Distress caused by the questionnaires: we are aware that some of the questions we ask may be embarrassing or even distressing to answer. If this is the case we can provide support for you through the clinical teams with whom we work. We will give you information about how to ask for this help when we give you the questionnaires.

Discomfort from testing pain-relevant systems: none of these tests will cause lasting damage, however, in order to fully assess systems relevant to pain we do need to cause some brief pain. The devices we use are designed to be as short as possible and to create the minimal amount of pain required to collect the data we need. If you wish to stop the study at any point you will be free to do so with no need to explain yourself and no implication for your current or future clinical care.

Brain scan (fMRI): MRI is safe and non-invasive and does not involve any ionising radiation (x-rays). However, because they use a large magnet to work, MRI scans are not suitable for everybody. Because of this, you will be asked to complete a pre-screening safety questions to help determine if you are able to take part. For example, if you suffer from claustrophobia, you could not be scanned. Normally, MRI scanning for research purposes would not be performed without further investigation if you have a heart pacemaker, mechanical heart valve, mechanical implant such as an aneurysm clip, hip replacement, or if you carry other pieces of metal that have accidentally entered your body. While there is no evidence to suggest that MRI is harmful to unborn babies, as a precaution, the Department of Health advises against scanning pregnant women unless there is a clinical benefit. We do not test for pregnancy as routine so if you think you may be pregnant you should not take part in this study. As some of the scans are noisy, we would give you earplugs, head padding or headphones to make this quieter for you. It is important that these are fitted correctly as they are designed to protect your ears. In preparation for your scan and for your comfort and safety we may ask you to change into pocketless and metal free "pyjama-style" top and trousers, which are available in a range of sizes. You may keep your underwear and socks on, but we would ask people to remove any bras as they often contain metal. If you have a soft sports bra without clasps you may wear this if you would prefer. Metal jewellery, including body piercing, must also be removed. Eye shadow and mascara must also be avoided, since some types contain materials that can interact with the magnetic field. If you wish to wear eye makeup to your scan we can provide makeup removal wipes but you are advised to bring your own makeup to reapply. Lockers are provided to secure your personal belongings and clothing. It is important to note that we do not carry out scans for diagnostic purposes, and therefore these scans are not a substitute for a doctor's appointment. Our scans are not routinely looked at by a doctor; rather our scans are intended for research purposes only. Occasionally a possible abnormality may be detected. In this case, we would have the scan checked by a doctor. If the doctor felt that the abnormality was medically important, you would be contacted directly and recommended to have a hospital (NHS) diagnostic scan arranged. All information about you is kept strictly confidential.

Heart rate measurement (ECG): ECG is safe and non-invasive. We record the information needed by placing 3 sticky tabs on one side of the ribcage and both sides near the collar bones. It is important to note that we do not carry out ECGs for diagnostic purposes, and therefore these ECGs are not a substitute for a doctor's appointment. Our ECGs are not routinely looked at by a doctor; rather our ECGs are intended for research purposes only. It is very unlikely that anything unusual would be detected on these measurements, however, very occasionally, a possible abnormality may be detected. In this case, we would have the ECG checked by a doctor. If the doctor felt that the abnormality was medically important, you would be contacted directly and recommended to

have a clinical (NHS) diagnostic ECG arranged. All information about you is kept strictly confidential.

What are the possible benefits of taking part?

You will receive no medical benefit from taking part in this study. However, we hope the findings from this study will be beneficial for young people and adults who menstruate and experience period pain or other chronic pain conditions.

Will my General Practitioner/family doctor (GP) be informed of my participation?

We will inform your GP if you are taking part in the study by sending them a letter. We will also write to them if we are concerned about any answers in the questionnaire. If we detect any anomalies in your MRI scan (a very rare occurrence) we will also contact your GP.

Will my taking part in the study be kept confidential?

Information obtained while you are in this study will remain strictly confidential (private) at all times. The way we do this is by using encryption (making the information unreadable to others), password protection, and keeping signed documents in locked cabinets. We will keep data in a secure research database, and you will be identified only by a study code. This means that personal information (like your name and address) will be held separately from samples, questionnaires and clinical information. Personal information will only be used to contact you as part of the study.

Responsible members of the University of Oxford and the appropriate NHS Trust may be given access to data for monitoring and/or audit of the study to ensure that the research is complying with applicable regulations.

Will I be reimbursed for taking part?

For the visits you need to travel to us, and we will reimburse your travel expenses. Additionally, you will receive vouchers for taking part, to say thank you for your time taking part in the study. A voucher of £25 will be given to you for each visit (there will be four visits in total, or 2 visits if not having brain scans), a £15 voucher will be given to you after you complete the first set of questionnaires and a final £25 voucher will be given to you if you complete the end of study questionnaire. If you participate in all aspects of the study, you will receive up to £140 worth of vouchers.

What will happen to the samples I give?

The saliva samples will be kept securely and confidentially (privately), and will be labelled with your unique study identification number. Samples will be referred to only by this study identity number, and your name will not be available to the laboratory investigators. Once we have collected samples from all the people in the study these will be stored until we are ready to analyse them. Some of the analysis may be performed by other laboratories including within commercial companies and therefore samples will be transferred from Oxford to these laboratories, this includes laboratories outside of the UK.

We will use large-scale analysis techniques to look at all of the different biological and genetic material found in your saliva. We will use this information in our analysis to see how hormones affect our measures. You can find more information about genetics on our website (www.wrh.ox.ac.uk/research/roadpain).

If you agree, part of the samples taken will be used for genetic studies, looking for variation across your entire genome, e.g. through DNA or RNA sequencing. Genes provide instructions for processes in the body and for traits such as eye colour. Everyone's genes are a little different. Information about these differences among people can help researchers understand things, such as how to best use drugs to treat disease. The results of these tests will not have any implications for

you personally. The results from your genetic tests will not be fed back to you and will only be used for research. These analyses are not the same as those that may be carried out in a clinical genetic screen for a specific disease-linked gene. All data including the genetic data will be coded before analysis so that researchers will not be able to link research results directly to individuals. However, your DNA is unique to you so it can never be completely anonymous. If you have any questions about this please let us know and we can talk to you about them.

What will happen to my data?

Data protection regulation requires that we state the legal basis for processing information about you. In the case of research, this is a task in the public interest. The University of Oxford is the sponsor for this study. It is the data controller and is responsible for looking after your information and using it properly. We will be using information from you in order to undertake this study We will use the minimum personally-identifiable information possible. We will keep identifiable information about you for up to 3 years after the study has finished, however, research documents containing personal information, such as consent forms, will be stored securely for 10 years. We will store the de-identified research data securely at the University of Oxford for 3 years after the youngest participants reaches 18 years old, or for 5 years, whichever is longer. Analysis of your data will be performed by a variety of members of the research team skilled in different areas. This will include students under the supervision of Prof Katy Vincent. We will not share any data collected with your parent(s)/carer(s).

The local study team will use your name and contact details to contact you about the research study and to oversee the quality of the study. They will keep identifiable information about you from this study for 12 months after the study has finished. However, if you give us permission to contact you about future relevant research, we will store your contact details longer. These will be stored separately from this study in a secure way at the local site. Agreeing to be contacted about future studies does not oblige you to participate in any other projects.

The coded genetic data and limited relevant details including, age, gender, information about your body type, biochemistry etc. can also be made available to collaborators and to the National Institute for Health Research (NIHR) Bioresource (http://bioresource.nihr.ac.uk/). This is a panel of thousands of volunteers, both with and without health problems, who are willing to be approached to participate in research studies investigating the links between genes, the environment, health and disease. You will be asked if you are happy to be re-contacted for future research studies either related to period pain or for other health studies approved by an ethics committee that access the NIHR Bioresource.

Data protection regulation provides you with control over your personal data and how it is used. When you agree to your information being used in research, however, some of those rights may be limited in order for the research to be reliable and accurate., Further information about your rights with respect to your personal data is available at https://compliance.web.ox.ac.uk/individual-rights. You can find out more about how we use your information by contacting katy.vincent@wrh.ox.ac.uk.

What will happen if I don't want to carry on with the study?

Taking part in this research study is voluntary. You may decide not to take part or you may stop at any time without giving a reason. It will not affect your medical care now or in the future.
If you do stop taking part in the study, no more data will be collected about you. We would ask your permission to keep your samples and data collected up to that point; however, it will be possible to destroy any samples still at the hospital if you ask us to do this.
If you lose capacity to consent during the study, you will be withdrawn from the study. Identifiable data or tissue already collected with consent would be retained and used in the study. No further data or tissue would be collected or any other procedures carried out with you.

What will happen to the results of this study?

The results of this study will be summarised in scientific articles that will be published and presented at relevant conferences, including meetings dedicated to gynaecology and pain. You will not be identifiable in any of these instances, and your details will remain strictly confidential (private). Some of the research being undertaken will also contribute to the fulfilment of an educational requirement (e.g. a doctoral thesis).

We would also like to feedback our findings to you. Summaries of the findings and all associated publications will be available on the project website: https://www.wrh.ox.ac.uk/research/roadpain/view and will also be placed on the websites of the partnering patient organisations: https://endometriosis-uk.org.

What if we find something unexpected?

None of the genetic or sample analyses are clinically useful and therefore we will not be feeding back any results from these. However, although the brain scans are not routinely looked at by a doctor and are intended for research purposes only, there is the possibility that an abnormality might be detected. As described above, if such an abnormality were found we would have the scan checked by a doctor who would then contact you directly to advise on the need for further investigations. We will also write to your GP if we are concerned about any answers in the questionnaires.

What if there is a problem?

The University of Oxford, as Sponsor, has appropriate insurance in place in the unlikely event that you suffer any harm as a direct consequence of your participation in this study. NHS indemnity operates in respect of any clinical treatment which is provided.

If you wish to complain about any aspect of the way in which you have been approached or treated during the course of this study, you should contact Prof Katy Vincent on katy.vincent@wrh.ox.ac.uk or you may contact the University of Oxford Research Governance Ethics and Assurances (RGEA) office on 01865 (6)16480, or the director of RGEA, email rgea.complaints@admin.ox.ac.uk.

How have patients and the public been involved in this study?

We have worked with patient representatives since we started designing this study and they are key partners in the project. More details regarding their involvement are available on the project website: https://www.wrh.ox.ac.uk/research/roadpain/view

Who is organising and funding the study?

This study is being organised by a group of researchers from around the United Kingdom, led by Prof Katy Vincent, Nuffield Department of Women's and Reproductive Health, University of Oxford. It is funded by the Medical Research Foundation as part of the UKRI Strategic Priorities Fund (SPF) Advanced Pain Discovery Platform (APDP), a co-funded initiative by UKRI (MRC, BBSRC, ESRC), Versus Arthritis, the Medical Research Foundation and Eli Lilly and Company Ltd. Oxford University is the Sponsor of this study.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect participants' interests. This study has been reviewed and given a favourable opinion by London-Bloomsbury Research Ethics Committee.

Further information and contact details:

Before, during or after the study, if you have any questions, please contact Prof Katy Vincent, Consultant Gynaecologist, who is leading the study. If you would like to be involved or would like more information to help you make this decision, please contact roadpain@wrh.ox.ac.uk

Thank you for taking the time to read and consider this information sheet.