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PARENT/GUARDIAN INFORMATION SHEET

RoADPain: Understanding the Importance of Period Pain in Teenagers

We would like to invite your child/ward 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 your child. There is no direct benefit to you or your child/ward for taking part, although they will be reimbursed for their time. Please take time to read this carefully and discuss it with friends, family or your GP if you wish. If there is anything that you do not understand, or if you would like more information, please ask us. Please take time to consider whether you wish your child/ward to take part.

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 has my child/ward been invited?

Your child/ward have been invited to take part in this study as they are aged 11-20, have had at least 6 periods a year since their periods started and have not used hormonal therapies (such as the pill or the mini-pill) in the past.

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.

Does my child/ward have to take part?

No. It is up to you if you want your child/ward to take part. We will describe the research, go through this information sheet with you and your child/ward, and answer any questions you and your child/ward may have. If you agree to take part, we will ask you to sign a consent form and your child/ward an assent form and will give each of you a copy to keep. However, you would still be free to withdraw your child/ward at any time, without needing to give a reason. This would not affect legal rights your child/ward would receive. If your child/ward is a student in the area of Oxford, there would be absolutely no academic penalty if you decide you do not want your child/ward to take part, or if you decide to withdraw your child/ward at any point. If you decide you do not want to take part this will not affect your or your child/ward's healthcare.

What will happen to my child/ward if they take part?

There are 4 main parts to this study and we ask your child/ward to take part in them all:

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

We will describe what happens in each part of the study separately. We will ask your child/ward 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 their menstrual cycle (once during their period and once around 10 days after a period).

We ask you as their parent/carer to come to all visits, although you will not be able to be with your child/ward for all parts of the testing (e.g. the brain scan) as having someone else in the room can alter our results.

1) Questionnaires

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

At each visit we will also ask your child/ward to fill out a short questionnaire about how they are feeling.

We will also ask your child/ward to complete another questionnaire at the end of the study, depending on our study results.

2) Saliva collection

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

3) Testing of pain relevant systems

The second part of the study will involve your child/ward coming in to the John Radcliffe Hospital at two different times. The timings of these will be around their menstrual cycle, with one session during their period and the other around 10 days after a period. These visits will take about 4 hours plus break times each. As the parent/carer you can be in the room whilst we explain what we will be doing and demonstrate/show equipment but we will ask you to step outside the room for the tests. This is because the presence of a parent/carer can alter the responses to our tests. Ideally we would like your child/ward to not drink caffeine or take painkillers on the day of the tests, but it is okay if this is not possible.

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 child/ward's non-dominant hand (if they are right-handed we will test on their left hand). For each sensation we will ask them to report what they felt. We will also test how they experience different sounds.

Part 2 assesses other systems that can alter pain including your child/ward's brain's ability to damp down painful sensations, their stress response and the function of their autonomic nervous system, which controls how fast their heart beats and their blood pressure. This part will last about 1 hour. Firstly, we will also ask for a saliva sample to measure their stress hormones. Then, we will stick pads to the top of their chest to take a tracing of your child's/ward's heart (an ECG) and put a blood pressure cuff around their arm. These will give us all the information we need about their autonomic nervous system. We will then ask your child/ward to sit quietly on a seat for about 20 minutes whilst we collect these readings. Next, we will test how they respond to some painful sensations. These will be short and will not cause them 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 your child/ward. Once we have finished these tests we will ask your child/ward 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 child/ward's bladder is. This will take up to two hours. About an hour before the test we will ask them to drink plenty of fluid to ensure they are well hydrated. When we start, we will ask them to go for a wee and we can then start the test. They will need to sit quietly in a room for the duration of this visit, but we will give them some puzzles to occupy them. We will give them a fixed amount of water to drink and then, at regular intervals, ask them to rate sensations from their bladder. When they feel their bladder is at its maximum fullness and they can't hold it any longer, we will ask them to go to the toilet to empty their bladder into a bowl. Then we will measure the volume. We will stop this part after two hours and ask them go to the toilet then if they haven't already. This may be a bit uncomfortable if it puts pressure on their 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 your child/ward 5 small bottles that we would like them to collect their saliva in the day before their next visit. We will give them instructions about how to collect these samples. We ask them to return these to us at the start of the next visit and we will put them in the fridge.

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

The third part of the study will involve your child/ward coming in to the John Radcliffe Hospital at two different times for a brain scan. The timings of these will be around their menstrual cycle, with one brain scan during their period and the other around 10 days after a period. As the parent/carer you

will not be able to be in the scanner with your child, although if necessary you may be allowed into the scan room, depending on safety procedures.

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

What should I consider?

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

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

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 your child/ward.

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 your child/ward through the clinical teams with whom we work. We will give your child/ward information about how to ask for this help when we give them 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 your child/ward wishes to stop the study at any point they will be free to do so with no need to explain themselves and no implication for their 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 and your child/ward will be asked to complete a pre-screening

safety questions to help determine if they are able to take part. For example, if they suffer from claustrophobia, they could not be scanned. Normally, MRI scanning for research purposes would not be performed without further investigation if they have a heart pacemaker, mechanical heart valve, mechanical implant such as an aneurysm clip, hip replacement, or if they carry other pieces of metal that have accidentally entered their 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/they think they may be pregnant they should not take part in this study. As some of the scans are noisy, we would give your child/ward earplugs, head padding or headphones to make this quieter for them. It is important that these are fitted correctly as they are designed to protect their ears. In preparation for their scan and for their comfort and safety we may ask them to change into pocketless and metal free "pyjama-style" top and trousers, which are available in a range of sizes. Your child/ward may keep their underwear and socks on, but we would ask people to remove any bras as they often contain metal. If they have a soft sports bra without clasps they may wear this if they 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 your child/ward wish to wear eye makeup to their scan we can provide makeup removal wipes but they are advised to bring your own makeup to reapply. Lockers are provided to secure their 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/your child/ward would be contacted directly and recommended to have a hospital (NHS) diagnostic scan arranged. All information about your child/ward 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 picked up. In this case, we would have the ECG checked by a doctor. If the doctor felt that the abnormality was medically important, you/your child/ward would be contacted directly and recommended to have a clinical (NHS) diagnostic ECG arranged. All information about your child/ward is kept strictly confidential.

What are the possible benefits of taking part?

Your child/ward 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 their General Practitioner/family doctor (GP) be informed of their participation?

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

Will their taking part in the study be kept confidential?

Information obtained while your child/ward is 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 they will be identified only by a study code. This means that personal information (like their name and address) will be held separately from samples,

questionnaires and clinical information. Personal information will only be used to contact you/your child/ward 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 my child/ward be reimbursed for taking part?

For the visits your child/ward needs to travel to us, and we will reimburse their travel expenses. Additionally, they 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 your child/ward for each visit (there will be four visits in total, or 2 visits if not eligible for fMRI scans), a £15 voucher will be given to them after they complete the first set of questionnaires and a final £25 voucher will be given to them if they complete the end of study questionnaire. If they participate in all aspects of the study, they will receive up to £140 worth of vouchers.

What will happen to the samples my child/ward gives?

The saliva samples will be kept securely and confidentially (privately), and will be labelled with your child/ward's unique study identification number. Samples will be referred to only by this study identity number, and their 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.

If you agree, part of the samples taken will be used for genetic studies, looking for variation across your child/ward's 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 your child/ward personally. The results from their genetic tests will not be fed back to you or them 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 your child/ward so it can never be completely anonymous. If you, or your child/ward, have any questions about this please let us know and we can talk to you about them.

What will happen to my child/ward's data?

Data protection regulation requires that we state the legal basis for processing information about your child/ward. In the case of research, this is a 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 child/ward's information and using it properly. We will be using information from your child/ward in order to undertake this study. We will use the minimum personally-identifiable information possible. We will keep identifiable information about your child/ward 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 child/ward's 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 your child/ward's data with you as a parent/carer.

The local study team will use your child/ward's name and contact details to contact you and them about the research study and to oversee the quality of the study. They will keep identifiable information about your child/ward from this study for 12 months after the study has finished. However, if you give us permission to contact you/your child/ward about future relevant research, we will store their 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 or your child/ward to participate in any other projects.

The coded genetic data and limited relevant details including, age, gender, information about your child/ward's 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 child/ward's personal data and how it is used. When you agree to your child/ward's information being used in research, however, some of those may be limited in order for the research to be reliable and accurate. Further information about their rights with respect to their personal data is available

at <https://compliance.web.ox.ac.uk/individual-rights>.

You can find out more about how we use their information by contacting katy.vincent@wrh.ox.ac.uk.

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

Taking part in this research study is voluntary. You may decide for your child/ward to not take part or you may want your child/ward stop at any time without giving a reason. It will not affect your child/ward's medical care now or in the future.

If your child/ward does stop taking part in the study, no more data will be collected about them. We would ask your permission to keep their 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 your child/ward loses capacity to assent during the study they will be withdrawn from the study. Identifiable data or tissue already collected with consent and assent would be retained and used in the study. No further data or tissue would be collected or any other procedures carried out on or in relation to your child/ward.

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. Your child/ward will not be identifiable in any of these instances, and their 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 child/ward's 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 your child/ward suffer any harm as a direct consequence of their 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 or your child/ward 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 has received funding from 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 your child/ward 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.