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**Participant Information Sheet**

**An investigation of the effect of sex on resolution of the inflammatory response in healthy volunteers: RESOLVE-SEX**

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**Invitation paragraph**

You are being invited to take part in a research study. Before deciding to take part it is important for you to understand why this research is being done and what it will involve. Please take time to read the following information carefully. Talk to others about the study if you wish.

One of our research team will go through the information with you to make sure that you understand. Ask us if there is anything that is unclear or if you would like more information or more time. Queen Mary University of London (QMUL) is the Sponsor of this research.

**What is the purpose of this study and what would taking part involve?**

It is now accepted that bias, in its many forms, plays a substantial role in our lack of understanding of coronary artery disease (CAD: blocking (furring up) of the arteries of the heart) initiation and progression in women. Whilst pre-menopausal women appear to be protected from CAD, women who suffer a heart attack (also known as an acute coronary syndrome [ACS]) have double the risk of further heart attacks compared to men, despite conventional treatment that works well in men. Women also experience much greater rates of heart attacks that occur without block of the arteries that feed the heart, than their age-matched male counterparts. Differences in biology between women and men is likely play an important role, however there is a lack of understanding of female physiology in this area due to a lack of research. Inflammation is important in the development of CAD and previous work from our laboratory showed that women appear to be better at resolving the process of inflammation compared to men. Whether problems in resolving inflammation underlies differences in CAD remains unknown. In this study we want to build on our previous work showing that healthy women resolve inflammation more effectively than men, we want to understand the underlying biological mechanisms for this. We are using a naturally occurring protein called cantharidin to cause mild and temporary inflammation in the skin. The cantharidin is applied to the skin of the forearm (or elsewhere) and a small (~2-3cm2) blister forms within 24h. The fluid in these blisters can be analysed to gain insights into the process of inflammation and resolution of inflammation.

**Visit 1 (~1.5 hr)-remote or in-person**

You will either attend the William Harvey Clinical Research Centre at Charterhouse Square for a screening visit or an online Teams/Zoom meeting at least 48 hours prior to commencing the study. Whether you attend this first visit in person or online is your choice. We will explain the study to you and we will interview you regarding your medical history including illnesses, medications, date of last period if female and recent vaccinations. A physical examination will be performed including height, weight, BMI, blood pressure and heart rate (this may be delayed to visit 2 if the screening is performed virtually). Female volunteers may be asked to perform a pregnancy test as the application of cantharidin is contraindicated in pregnancy. If you fulfil the screening criteria, you will be invited to sign the consent form (this will be signed at visit 2 if a virtual screening). You will need to come to the centre on 4 occasions for the study over a period of 4 consecutive days.

**Visit 2 (~1.0 hr)**

You will be asked to fast 3 hours prior to visit 2 and should avoid caffeine entirely on this day. Your blood pressure will be measured every 5 minutes for 15 minutes. Blood (approximately 20mL – four teaspoons), urine and saliva will be collected. A single application of cantharidin will be applied to your forearm, back or abdomen (by a train physician) depending on your preferred place. A photograph of the blister location will be taken on a dedicated laboratory camera. It will not be possible to identify you from the photograph and this will be stored securely. A dressing will be applied which will be left in place and should be kept dry until blister fluid is sampled.

**Visit 3 (~0.5 hr)**

24 hours after visit 2 you will return and have cantharidin applied to a separate area, no less than 5 cm away from the initial application in visit 2. A photograph of the blister location will be taken on a dedicated laboratory camera. It will not be possible to identify you from the photograph and this will be stored securely. A dressing will be applied to the second blister which will be left in place and should be kept dry until blister fluid is sampled.

**Visit 4 (~0.5 hr)**

48 hours after visit 2 you will return to have cantharidin applied to a separate area, no less than 5 cm away from the first two applications in visit 2 and 3. A photograph of the blister location will be taken on a dedicated laboratory camera. It will not be possible to identify you from the photograph and this will be stored securely. A dressing will be applied to the third blister which will be left in place and should be kept dry until blister fluid is sampled.

**Visit 5 (~1.5 hr)**

72 hours after visit 2 you will return. You will be asked to fast 3 hours prior to this visit and should avoid caffeine entirely on this day. During visit 5 your blood pressure will be measured again. Dressings will be removed and a photograph of the blister locations will be taken on a dedicated laboratory camera. It will not be possible to identify you from the photograph and this will be stored securely. The blister fluid will be sampled (by carefully piercing the side of the blister and collection of the fluid contained within the blister). Blood (approximately 20mL – four teaspoons), urine and saliva samples will be collected. The blister remnants will be dressed with gauze. In order to help with the healing process, you should try to keep the area as dry as possible until the blister has sealed which will usually take a few days. The blister roof should also be left in place to aid in healing. Further gauze will be provided to allow you to change the dressing if needed.

**Visit 6 (~15 min)-Remote**

We will conduct a telephone interview 28 days following visit 1 to check if there have been any adverse reactions or events.

By agreeing to tissue storage, you will only be giving us permission to store your blister samples, blood, saliva and urine for future research of the type described above. Any other use that we may want to make of your sample in the future will require approval by a Research Ethics Committee, which is an independent panel of experts who assess all research projects for safety, ethical acceptability and who protect volunteers’ interests. During the storage of the samples, all of the information regarding you will be kept strictly confidential and the samples will be anonymised. Only the investigators and research monitors will have access to the data. Your samples will not be transferred outside the UK and there will be no genetic testing, use of animals or commercial involvement with your samples. Any future use of these samples will require prior approval by the Research Ethics Committee as described above. None of the work that we envisage will have any direct implications for your personal health. You do not have to agree to the storage of your tissue. You are free to decide not to participate.

A short summary of the study findings will be available when the study has been completed and the data has been analysed by the research time. If you wish this can be made available to you by email and you will be asked whether you would like this during the consent process.

**Why am I being invited?**

You have been chosen because you are healthy and well. 34 volunteers will be recruited into this study.

**Do I have to take part?**

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 asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will have no adverse consequences (if you are a student, this will not affect your course of study). You will still receive your full payment for your participation in whichever parts of the study you have commenced, even if you withdraw before it finishes. Information and samples already gathered will be destroyed/disposed of.

**What are the possible benefits of taking part?**

The main benefits of this study is that it will provide greater understanding of the process of inflammatory resolution in humans and a greater understanding of why women appear to be more efficient at resolving inflammation. We hope that through the information gained from this study it may provide the basis for future research into new treatments for people with heart disease.

**What are the possible disadvantages and risks of taking part?**

The risks in this study are negligible. Taking blood samples may cause mild bruising/pain, to minimise the risk of this, blood sample acquisition will only be carried out by experienced individuals. Cantharidin may cause some mild discomfort whilst the blister is forming. In previous studies using Cantharidin there have been no permanent adverse effects with any scars or pigmentation disappearing by 26 weeks, providing volunteers adhere to the guidance we provide to take care of the blisters from bursting. From our previous observations we have noted that the process of scar/pigmentation disappearance may take longer (up to 4 months) in non-Caucasians. Once the cantharidin is applied the area will be dressed and the blisters protected. We will provide guidance to all volunteers on how to protect the blisters from bursting. Our previous evidence indicates that the recovery time from burst blisters is substantially longer.

**Expenses and payments**

Once you have been screened and consented for the study, a payment of £130 will be made if you complete all of the physical visits, if you choose to withdraw from the study early a payment of £30 per physical visit will be made. We also reimburse reasonable travel expenses within Zone 6 in London, on provision of receipts. Travel from outside this area needs to be agreed with the investigators in advance. Payment is by cheque of bank transfer (payable from Barts and the London Faculty of Medicine and Dentistry): this may take 2-3 weeks; or may be made in cash on the day, depending on the arrangements at the time. Payment is for undergoing the study and not for us taking and storing your blood. Payment is therefore not dependent on you agreeing to tissue retention (blood, urine and saliva samples).

**What information about me will you be collecting?**

As outlined in a screening visit we will take information about your medical history to ensure you are healthy and eligible for the study. When you enter into the study we will record your blood pressure. Blood samples will be collected which will be analysed for routine haematological, biochemical markers as well as oestrogen, FSH and testosterone levels. We will also assess the levels of markers of your inflammatory status within these samples. We will assess nitric oxide levels (a substance in the body important for function of blood vessels) in your blood, urine and saliva. The blister fluid obtained will be analysed for various cells and signalling markers for inflammation. We will also collect a saliva sample for bacterial DNA and human DNA analysis that will be conducted at a later date. This analysis will only be performed on anonymised samples for submission to a biobank, therefore it will not be possible to link these results to you.

**How will my data be stored and who will have access to it?**

We will follow the NHS Code of Confidentiality. Data will be handled in accordance with GDPR and DPA 2018. Your name and other identifiers will be replaced by a unique code to reduce the risk of disclosure. There will be a key document which will link your unique code to your real identity which will be stored securely and separately from the rest of your research documents. Personal information will only be used on the consent form and on the unique code. Personal information will be used to contact you if needed and to remind you of study dates. Any paper records will be stored/accessed for 12 months-3 years after the study has ended. These will be kept in a locked cupboard within a locked office or clinical room. Most of the research data will be stored electronically on password protected computers at the William Harvey Clinical Research Centre. Members of the research team involved in this study will have access to this data. Any information sent electronically amongst the research team will be encrypted. Fully anonymised data will eventually be shared with fellow researchers via conference presentation and via publication in scientific journals.

**When and how will my data be destroyed?**

Paper records will be stored/accessed for 12 months-3 years after the study has ended. When the research trial is complete, research findings will be stored in the Modern Records Facility at 9 Prescot street, London, E18PR, as per sponsor’s policy. Research data generated by the study will be stored for 25 years.

**How will my data be used and shared?**

Research data described above will be shared amongst the research team involved in this study for the purposes of analysis. Any information shared electronically between the team will be encrypted. Fully anonymised data will eventually be shared with fellow researchers via conference presentation and via publication in scientific journals. This study also forms part of a PhD project and therefore data will be used in the production of a PhD thesis.

**Under what legal basis are you collecting this information?**

Queen Mary University of London processes personal data for research purposes in accordance with the lawful basis of ‘public task’.

Please read [Queen Mary’s privacy notice for research participants](http://www.arcs.qmul.ac.uk/media/arcs/policyzone/Privacy-Notice-for-Research-Participants.pdf) containing important information about your personal data and your rights in this respect. If you have any questions relating to data protection, please contact Queen Mary’s Data Protection Officer, Queens’ Building, Mile End Road, London, E1 4NS or data-protection@qmul.ac.uk or 020 7882 7596.

**What will happen if I want to withdraw from this study?**

You are free to withdraw from the study at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will have no adverse consequences (if you are a student, this will not affect your course of study). You will still receive your full payment for your participation in whichever parts of the study you have commenced, even if you withdraw before it finishes. Information and samples already gathered will be destroyed/disposed of.

**What should I do if I have any concerns about this study?**

If you have any concerns about the manner in which the study was conducted, in the first instance, please contact the researcher(s) responsible for the study Dr Andrew J Sullivan, Dr Krishnaraj S Rathod or Prof Amrita Ahluwalia [Principal Investigator]. If you have a complaint which you feel you cannot discuss with the researchers then you should contact the Research Ethics Facilitators by e-mail: research-ethics@qmul.ac.uk. When contacting the Research Ethics Facilitators, please provide details of the study title, description of the study and reference number (where possible), the researcher(s) involved, and details of the complaint you wish to make.

**Who can I contact if I have any questions about this study?**

If you require any further information please contact

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