Participant Information Sheet (PIS)

Title of the study: Exosome release following a single bout of cycling exercise in chronic kidney disease – the ENCODE study

Chief Investigator: Dr Emma Watson (University of Leicester, Department of Cardiovascular Sciences)

You are being invited to take part in a research study. Before you decide, 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. Ask us if there is anything that is not clear, or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

Chronic Kidney Disease (CKD) is a growing health problem across the world, with approximately 5% of the UK population having lost some kidney function. A common complication of CKD is heart disease, or cardiovascular disease (CVD), which is the biggest cause of death in this population. However, we do not have any treatments for CVD that are specifically for kidney patients, which is important because the causes of heart disease are different in CKD. This means we are unable to reduce the number of people that develop CVD, or importantly, reduce deaths. Therefore, there is an urgent need to develop tailored treatments to treat heart disease specifically for the CKD population.

Given the known health benefits of exercise, our group undertook the CYCLE-HD study to see if cycling during dialysis could improve the health of people's hearts. This study showed that people who took part in the 6-month cycling programme had improvements in heart structure compared to those who received their usual care. However, the level of exercise that people were able to do was very low, much lower

than you would expect, and so the factors that led to these improvements in heart health are unknown. Knowing this information will help us to develop other treatments that are also able to give the same benefits as the exercise did, which is important because not all patients are able, or want to take part in exercise.

Here we will test a new idea that these improvements could have been caused by cellular cross-talk. This means that one tissue like the muscles, may release some genetic information in the form of very short pieces of RNA known as microRNAs, in something called exosomes following exercise. Exosomes are very small vesicles that are released from most cells, they travel in the blood and are taken up by another organ, like the heart, where they have beneficial effects. The field of cellular cross-talk is a relatively new and exciting field of cellular biology and the use of exercise derived exosomes has been proposed as a potential new treatment for diabetes and obesity.

The aims of this study are to determine if microRNA's are released from skeletal muscle following cycling in patients with CKD, and if they may have played a role in the improvements in heart health that were seen following training in the CYCLE-HD study.

Why have I been invited to participate?

You have been invited because you are currently undergoing haemodialysis treatment.

Altogether we will invite 15 participants to take part.

Do I have to take part?

No, taking part is voluntary. 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 asked to sign a consent form. You are free to withdraw at any time and do not need to provide

a reason. A decision to withdraw, or a decision not to take part will not affect the standard of any care you receive. If you lose the capacity to consent for any reason, we will withdraw you from the study, but any data and samples that we have collected up to that point will be kept.

What will happen to me if I take part?

If you decide that you would like to take part, we will invite to the hospital on non-dialysis days two occasions, at your convenience to take part in some short physical tests and some cycling exercise.

We will first ask you to sign a consent form to confirm that you are happy to take part in the study. We will then ask you to take part in the following assessments, or to provide the following information:

Demographic and clinical information (Visit 1)

This will take approx. 5 minutes

We will collect and record your initials, date of birth, gender and ethnicity. We will also access your medical records to collect information about your kidney disease, how long you have been on dialysis for, any medications that you are taking and any other illnesses or conditions that you may have. In order to do this, we will ask you to fill in a demographic questionnaire, and researchers will access your medical records.

Tests of physical function (visit 1)

Incremental Shuttle Walk Test (ISWT)

This will take approx. 20 minutes

You will be asked to walk around two cones placed on the floor 9 metres apart, at a speed timed by a recorded bleep sound. The bleep signal gets a little faster every minute so that you have to increase your walking speed to keep up. The test is stopped when you can no longer walk fast enough to keep up with the bleep. This test measures your maximum physical capacity.

Endurance Shuttle Walk Test (ESWT)

This will take approx. 15 minutes

From the result of the ISWT we will calculate a walking speed that equates to 85% of your maximum speed. We will then ask you to walk at this 85% speed (in time with a steady bleep) for as long as you can. The test is stopped when you can no longer keep walking at that speed. This test measures your stamina. Before doing both of these tests, you will be taught how to do it and allowed to practice.

Short Physical Performance Battery (SPPB)

This will take approx. 30 minutes

The SPPB measures balance, how fast you walk and your ability to stand from a chair. The SPPB has 3 parts

a. Chair stands - you start from a seated position on a hard, upright chair (such as a dining chair), with the feet flat on the floor and the knees bent at 90°. For the test, the time taken for you to stand up fully and then returning to sitting 5 times, without using the hands, is measured.
b. Standing balance tests in three progressive positions. If you are able to complete 10 seconds in the first position then you progress to the next stage as described below:
    - Feet together
    - Semi-tandem (one foot in front of the other but slightly out to the side, as if taking a step forward)
    - Tandem (one foot in front of the other, like walking a tightrope)
c. Gait speed – the time you take to walk 4m on a level course. It is measured a second time after a short break.

After completion of these assessments we will firstly demonstrate the cycling exercise that we wish to investigate the response to, and give you the opportunity to practise. We will then invite you back on a separate day to perform the exercise again at which time we will also collect blood samples.

Cycling Exercise (visit 1 and visit 2)

This will take approx. 30 minutes

On two occasions we will ask you to take part in cycling exercise on a static bike.

The first time that we do this, it will only be a practise and will be for you to get used to the exercise. During the cycling we will show you something called the 'rating of perceived exertion', or RPE for short, that is used to help people judge how hard they find the exercise. Depending upon your response, we will either make it easier or harder to get the exercise to an intensity that you think feels 'somewhat hard'. This is often explained to feel that you are out of breath a bit, but still able to hold a conversation. In order to make the exercise easier or harder we will change the resistance on the wheel that will make it either easier or harder to pedal. Once you feel that you are familiar with the exercise and the RPE scale you can stop the exercise.

The second time we ask you to do this will be on a separate visit to the hospital, and this time we will ask you to aim for 30 minutes of continuous cycling. After a 5-minute warm-up, we will set the resistance to the level we identified during the previous practise session that you found 'somewhat hard'. After a few minutes, and throughout the 30-minute period, we will show you the RPE scale again to make sure the exercise intensity is not too hard and not too easy. Whilst we will aim for 30 minutes of exercise, you will be able to stop at any time if you feel that you are not able to continue.

Blood samples

This will take approximately 10 minutes

During your second visit we will take 6 blood samples. To avoid lots of individual blood samples, we will insert a cannula (a small tube) into your arm and all blood samples will be taken through this. The first sample will be when you are resting before you have done any cycling. The remaining samples will be at different time points after you have stopped cycling – immediately after, 10, 30, 60 and 90 minutes after stopping. At each timepoint we will collect approximately 10ml of blood (about 2 teaspoons). We will use this to look at small molecules in your blood called exosomes, and will try to see what they contain. We will also look at some additional things like your lipid profile (e.g., cholesterol levels) and levels of inflammation. With your consent, some of the blood will be stored at the University in a research tissue bank for analysis in the future.

What will happen to any samples that I provide during and after the research?

All blood samples that we take will be transported back to the research group's laboratory at the University of Leicester. We will look at the exosomes and the small RNA molecules that are contained within them. We may send some of the samples to another organisation, for example Novogene who are based in Cambridge. They can perform a special type of analysis call 'sequencing' on them. This will let us compare your six different samples to see how the exosomes, and the things they contain, have responded to exercise. Sequencing will not be able to give us any information about your health, or that might indicate disease. It is also possible that we send samples to Affinity Biosciences for analysis of circulating cytokines. Cytokines are small molecules that are released from immune cells and certain tissues, including muscle, which are involved in the way that we adapt to exercise to get fitter. Analysis of cytokines within your samples will provide us with information about whether this response is different in people with CKD and may help us better design exercise programmes for these individuals. These samples may be sent to these companies during the ENCODE study, or during future ethically approved research.

Any tests carried out on the samples collected are part of a research programme and will not be used as a basis for diagnosis or treatment, either now or in the future. There

is a very small risk of identifying clinically significant abnormalities during the study. If this happens the consultant responsible for your usual care will be informed.

At the end of the ENCODE study, with your permission, we would like to keep any remaining blood samples (in their coded form) and enter them into a tissue bank.

For this type of study, we will store your research data and any research documents with personal information, such as consent forms, securely at the University of Leicester for 6 years following the end of the study. If you give us permission to retain your samples for future research, it is necessary to retain your consent form until the samples have been depleted or destroyed, or if you withdraw your permission. This may be longer than 6 years. If your samples are used up within this period, your consent form and personal information will be destroyed at the end of 6 years.

The Human Tissue Authority is the regulatory authority responsible for the oversight and Inspections of human tissue storage in the UK after a study has concluded. We require your consent form to comply with the Human Tissue Authority to ensure we have obtained your permission to retain the samples beyond the life of this project. Your consent form would be stored independently from your coded samples to ensure that the people who analyse the samples cannot identify you.

What are the main disadvantages and risks of taking part?

The main disadvantage of taking part is the time commitment involved attending the hospital for the additional visit or visits, but we will reimburse you for your travel expenses and can provide a taxi up to a value of £25 per visit. Please retain original receipts.

You may feel a bit uncomfortable when doing some of the physical function tests and find them hard, but we will give you plenty of rest between tests and attempts, and you can stop them at any time. Our group and the researchers involved in the study have lots of experience in doing them with patients. As with all physical activity, there is a

very small risk of accident or injury during the assessment visits and during the cycling exercise sessions. You will be supervised by a member of the research team at all times and if you feel any pain or discomfort we will ask you to stop. All the exercise will be supervised by trained research staff and will take place on NHS premises. We will ask you to wear comfortable clothing and trainers for both your study visits.

Although you may have had many blood tests before, sometimes taking blood samples may cause slight pain or some bruising afterwards, but is not dangerous. To reduce the bruising and pain from lots of blood samples we will put a cannula in your arm from which all the blood samples will be taken.

What are the possible benefits of taking part?

There are no direct benefits to taking part in this research. We hope that the results of the study will help us design improved treatments to reduce cardiovascular risk in people undergoing haemodialysis and for those who have chronic kidney disease that do not yet need dialysis.

What happens when the research study stops?

If you are receiving ongoing care, this will continue as usual and will not be changed.

What if something goes wrong?

If you have a concern about any aspect of this study, you should ask to speak with a member of the study team who will do their best to answer your questions. If you have concerns about any aspect of the way you have been approached or treated during the course of the study, you may wish to contact the hospital's Patient Information and Liaison Service (PILS). Contact details for the research team and PILS office can be found below. If you remain unhappy and wish to complain formally, you can do this through the NHS complaints procedure. Details can be obtained from the PILS office or from the hospital.

It is very unlikely that you would be harmed by taking part in this type of research study. In the event that something does go 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 against University of Leicester but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you (if appropriate).

pils.complaints.compliments@uhl-tr.nhs.uk.
The Firs, c/o
Glenfield Hospital,
Groby Road,
Leicester.
LE3 9QP
Freephone: 0808 1788337

Will my taking part in this study be kept confidential?

While you are taking part in the study, your contact details will be made available to the researchers so that they can contact you to arrange the details of your research study appointments. On the consent form, you can also choose to be informed about the results of the trial. If you consent for this to happen, we will store your contact details securely, separately from your survey form and clinical information, and we will only use them for the purposes you have chosen. Your contact details will be destroyed once they have been used for the purpose that you have agreed to. The study is taking place for 3 years. Anonymised research data will stored for 6 years after the study has finished.

Your data may be accessed by authorised individuals from the Sponsor (University of Leicester), regulatory authorities, and the host NHS organisation, for monitoring and audit purposes. We have a duty of confidentiality to you as a research participant and we will do our best to meet this duty.

You should be aware that we have a professional and ethical duty to act on concerns for your safety and welfare. If we identify welfare issues, such as deteriorating illness

or concerns of abuse, we may need to report these to your GP, your hospital team, or social services. We will tell you if we do this.

With your permission we may share your research data and/or samples with other academic or commercial organisations. These may be inside or outside the UK where data protection laws may differ. However, the sharing of data and/or samples will require a contract between the University and the receiving organisation and part of that contract will require them to follow our instructions about how to look after your data and/or samples carefully. Any data and/or samples will be shared in a way that you cannot be identified by the recipient.

How will we use information about you?

We will need to use information from you and from your medical records for this research project.

This information will include your:

- Name
- Gender
- NHS number and hospital number
- Date of Birth
- Ethnicity
- Phone number and email address
- Medical information about your illness
- Medicines that you are taking

We will use this information to do the research or to check your records to make sure that the research is being done properly.

People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead.

We will keep all information about you safe and secure.

Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

What are your choices about how your information is used?

You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have.

If you choose to stop taking part in the study and you are a patient with a long-term condition, we would like to continue collecting information about your health from your hospital records. If you do not want this to happen, tell us and we will stop.

We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.

If you agree to take part in this study, you will have the option to take part in future research using your data saved from this study.

Where can you find out more about how your information is used?

- On the following websites: www.hra.nhs.uk/information-about-patients/ and www.le.ac.uk/patient-gdpr-guidance
- by asking one of the research team
- by contacting us via the e-mail address or phone number at the end of this sheet
- by contacting the University's Data Protection Officer via email on dpo@le.ac.uk

What will happen to the results of the research project?

The data collected as part of this study will be used, in part or in whole, for the writing of educational projects such as a Master's Degree or a PhD.

We will publicise the results in posters and leaflets in clinical areas so you can read them while if and when you are there. If you would like us to send you a written report of the results, please sign the appropriate box on the consent form and we will send these to you as soon as they are available.

The results will also be published in a medical journal. All information will be anonymised so you will not be identified in any report or publication.

What should I do if I want to take part?

If, after reading this information sheet you think you may like to take part, please contact a member of the study team, our contact details are at the end of this information sheet. You will be asked to complete an Informed Consent Form and to opt-in to a variety of research options by placing your initials within the Yes or No box. This will confirm you understand how your data will be processed, protected and reviewed for research purposes.

Who is organising and funding the research?

The research is being organised by Dr Emma Watson and staff at the Centre for Sarcopenia and Muscle Research at the University of Leicester and funded by a research students bench fees.

Who has reviewed the research project?

All research that involves NHS patients or staff, information from NHS medical records or uses NHS premises or facilities must be approved by an NHS Research Ethics Committee before it goes ahead. This research was approved by the London – Surry Research Ethics Committee. Approval means that the committee is satisfied that your rights will be respected, that any risks have been reduced to a minimum and balanced

against possible benefits and that you have been given sufficient information on which to make an informed decision.

Thank you for taking the time to read this information and consider taking part in this research

Contact for Further Information

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