Participant Information Sheet

Version No. 6, 22/03/2024

Title of project: A randomised controlled feasibility trial of exercise for improving insulin sensitivity, inflammation, and metabolic health in postmenopausal women with overweight or obesity receiving chemotherapy for breast cancer.

Approval Numbers; IRAS: 326069, RWH: Trust XXXXXXXX, UoW 0123UOWSSC

Principal investigator: Dr Ravi Dandamudi

Chief investigator: Dr Ian Lahart

You are invited to participate in a research study titled: A randomised controlled feasibility trial of exercise for improving insulin sensitivity, inflammation, and metabolic health in postmenopausal women with overweight or obesity receiving adjuvant therapy for breast cancer.

You have been invited to participate as you match the criteria of participants we are recruiting for this study (female, post-menopause, classified as being overweight or obese, diagnosed with breast cancer, and due to be initiating chemotherapy treatment soon).

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. Take time (within 48 hours or 2 days of receiving this invite) to decide whether you want to participate in this study. If anything is unclear or you would like more information, please contact Hazel Shanley (h.a.shanley@wlv.ac.uk).

What is the purpose of the study?

This study aims to investigate the feasibility and effectiveness of a single bout of exercise before chemotherapy and a physical activity intervention for improving insulin sensitivity for women with breast cancer who are both postmenopausal and overweight/obese. Breast cancer is most common in women of menopausal age (45-69). Additionally, in postmenopausal women with breast cancer, obesity is associated with unfavourable treatment outcomes post-diagnosis. High insulin levels are common in people who are overweight or obese and in those undergoing cancer treatment,

which can contribute to increased risks of death and distant recurrence. There is sufficient evidence supporting the role of exercise in improving numerous health outcomes in breast cancer patients. For younger breast cancer patients and overweight and obese populations, we know that exercise helps to reduce insulin levels and increase insulin sensitivity. However, little evidence exists on whether exercise influences insulin and other biological markers in postmenopausal overweight or obese breast cancer patients.

Therefore, in the study population (postmenopausal overweight or obese breast cancer patients. We are aiming to:

1) Investigate patient responses after they have participated in a single exercise session before the initiation of treatment.
2) Evaluate the effectiveness of a 12-week exercise intervention on insulin resistance and related metabolic outcomes, treatment-related outcomes, body composition, and inflammation in patients receiving adjuvant chemotherapy for breast cancer treatment.

Why have I been chosen?
You have been invited as you are:

- A woman diagnosed with breast cancer.
- Categorised as post-menopause phase.
- BMI classification of 25-39.9 kg/m2 or 23-39.9 if you are Asian/South Asian.
- Due to be initiating chemotherapy treatment soon.

Do I have to take part?
No. Taking part is your decision. If you decide to participate, you will be given this information sheet to keep and asked to sign a consent form. If you choose to participate, you are free to withdraw at any time and without reason. If you wish to withdraw your data, you can do so by contacting Hazel Shanley (h.a.shanley@wlv.ac.uk).

What do I have to do?
Before the study begins, you will be randomly allocated to either an “exercise + standard care” group (exercise group), or a “non-exercise + standard care” group (control group). The allocation to either of the two groups is conducted by random computer selection, not by choice or manually assigned by the researcher. Participation in this study will involve an initial visit to the University of Wolverhampton, Walsall Campus.

If you are allocated to the exercise group, this study will involve a single exercise session before your first chemotherapy infusion and a 12-week exercise intervention (described below) during your treatment. We will measure a number of different outcomes before and after the exercise and chemotherapy infusion and then again during and after the 12-week intervention. These outcome measures will include insulin/glucose levels, oestrogen levels, adiponectin levels, leptin levels, markers of inflammation, levels of body fat, quality of life, and chemotherapy-related outcomes.

Single exercise session: You will be asked to perform a single session of supervised exercise 24-48 hours prior to the administration of your first chemotherapy dose. The

exercise session will take place at the University of Wolverhampton, Walsall Camus exercise facility and will be supervised by an experienced exercise and cancer specialist. This exercise session will have a duration of 50-60 minutes and will consist of an explanation of the session (5-10 minutes), a warm-up (5 minutes), continuous exercise (30 minutes), and cool down (10-15 minutes). The intensity (how hard) of the exercise session will be set at a 'vigorous intensity' based on the results of your exercise testing, so, the exercise intensity will be tailored to you and your abilities. Your heart rate will be monitored throughout this session, and we will also measure oxygen saturation using a small device connected to one of your fingers (pulse oximeter) throughout the exercise session.

12-week intervention: This study involves a 12-week intervention where participants assigned to the exercise group will partake in a chemotherapy-periodised exercise programme. Based on your scheduled chemotherapy cycles, the exercise intervention will be split into training blocks. For example, if you are scheduled for four 3-week cycles, the training blocks will be divided into weeks 1-3, 4-6, 7-9, and 10-12. The training programme will consist of two 60-minute supervised mixed exercise sessions and one 30-minute unsupervised but monitored aerobic exercise session per week.

Each supervised session will include an aerobic exercise component followed by progressive resistance training exercises. The intensity of these aerobic exercise sessions will be individually tailored, based on the results of your exercise testing. The week immediately following your chemotherapy infusion will be considered a 'de-loading week' where training intensity will be reduced. Over the course of the other weeks, we will aim to progressively increase the intensity from a moderate intensity to a vigorous intensity by the end of the intervention. Similarly, for the resistance training component, the week immediately following your chemotherapy infusion will be considered a 'de-loading week' where exercises will be set at a lighter intensity. In subsequent weeks, we will aim for a progression in weight and repetition numbers until the end of the intervention (weight and repetition numbers increasing alternatively each week). Exercise weights will be determined by your strength testing results at the start of the study. Supervised exercise sessions will be conducted at the University of Wolverhampton's fitness facilities on the Walsall Campus. These sessions will be supervised by appropriately trained exercise professionals and cancer and exercise specialists.

Unsupervised sessions will comprise a 30-minute walk performed on a day separate from the supervised sessions and at the convenience of each patient. The supervised and unsupervised exercise sessions combined provide a total of 150 minutes of exercise per week, aligning with current exercise and cancer guidelines.

<u>For those allocated to the control group</u>, you will continue your medical care without an exercise intervention for the duration of the study. We will still measure a number of different outcomes over the 16-week period during your chemotherapy treatment. These outcome measures will include insulin/glucose levels, oestrogen levels, adiponectin levels, leptin levels, markers of inflammation, levels of body fat, quality of life, and chemotherapy-related outcomes. Following the completion of the study, you will be offered an exercise service at The University of Wolverhampton, Walsall Campus fitness facilities.

Participants in both groups will undergo the same level of physical activity and dietary assessments. All participants will be provided with an activity tracker (HR monitor watch) for the duration of the study (smartwatches will need to be returned at the end of the study). Watches will be provided by the University of Wolverhampton and will replace any watches damaged or lost during the study. After completion of the study, watch memory will be wiped, reset, and used in other trials. The procedures of tests you will be undergoing are detailed in the 'Procedure Information Sheet'.

How long will the study last?
The study will last approximately 14 weeks from baseline testing to final testing session.

Will I be required to attend sessions, and where will these be?
All assessments and supervised exercise sessions will be held at the University of Wolverhampton, Walsall Campus.

If you are allocated to the control group: You will be asked to attend 3 sessions (initial visit, post-first chemotherapy visit, and a post-12-week intervention assessment).

If you are allocated to the exercise group: You will be asked to attend 28 sessions (an initial visit, a pre-chemotherapy exercise session, post-first chemotherapy visit, 24 supervised exercise sessions, and a post-12-week intervention assessment) in addition to completing 12 unsupervised at-home exercise sessions.

Preliminary visit (Consent and Familiarisation): On the first of your visits to the University of Wolverhampton, Walsall Campus, a member of our research team will recap the information within this document, and you will be given the opportunity to ask any questions that you may have. If and when you are happy with the details of the study, a consent form will be signed. You will be provided with a Withings Steel smartwatch to wear for the duration of the study period. Once consent has been obtained, we will measure for a variety of outcomes. These tests will include an Oral Glucose Tolerance Test (OGTT), blood sampling, body composition, and fitness testing (see the Procedure Information Sheet).

Image: Gas Metalyser Mask used to collect gas samples during exercise testing.

Post-chemotherapy testing: in the 24 hours following your first chemotherapy infusion, we will repeat the oral glucose tolerance tests and blood sampling to explore changes in insulin sensitivity and pro- and anti-inflammatory biomarkers (see the Procedure Information Sheet).

Post-intervention assessments and semi-structured interviews (interviews for exercise group only): We will repeat the OGTT, blood sampling, and ventilatory threshold, muscular strength, anthropometric and body composition, and quality of life assessments for the final time. We will conduct qualitative semi-structures interviews with 15 patients from the Exercise Group to uncover their experience of the overall process.

Will travel costs be reimbursed?
We will reimburse participants for travel costs incurred and provide participants with refreshments after each testing session.

What are the possible disadvantages and risks of taking part?
The most obvious risks to you will involve fatigue or muscle aches from the exercise you experience after attending the gym or going for a brisk walk. Additionally, you may experience inconvenience due to blood sampling, e.g., the insertion of a needle used to obtain the blood samples can sometimes cause mild discomfort; however, all of the researchers involved are trained, skilled phlebotomist and will do their utmost to prevent this. Once the needle is positioned, you should be largely unaware of its presence, as blood extraction is painless. After removing the needle, there is a chance that a small amount of bruising may occur at the insertion point. After removing the needle, the researcher's application of pressure to this site will help reduce this risk.

Finally, if at any point during the protocol, you feel uncomfortable or unable to continue, testing will be ceased immediately.

What are the possible benefits of taking part?
By participating in this study, you will undertake a supported, structured exercise intervention, which should improve your fitness and health if adhered to. You will also receive a vast range of physiological, metabolic, and anthropometric information about yourself and your body. Such information is not only of great interest but could help guide you toward improving aspects of fitness and health in the future.

This study's findings will help us understand bodily responses to exercise in breast cancer patients who are both postmenopausal and overweight or obese. This may help to understand processes and mechanisms that improve breast cancer outcomes for this group of patients.

What if something goes wrong?
There are no special compensation arrangements if you are harmed by participating in this research project. If you are harmed due to someone's negligence, you may have grounds for legal action. Regardless, if you wish to complain or have any concerns about any aspect of how you have been treated during the course of this study, then you should immediately inform the Investigator (h.a.shanley@wlv.ac.uk). If you wish to seek some independent advice, then the Patient Advice and Liaison Services (PALS) are also available to you at the following address: PALS Office, The

Royal Wolverhampton Hospitals NHS Trust, New Cross Hospital, Wolverhampton WV10 0QP, Telephone number 01902 307999.

How will we use information about you?
In this research study we will use information from you. This information will include:

- Your name,
- Contact details,

People 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 research data so we can check results. We will write our reports in a way that no-one can work out that you took part in the study.

What are my choices about how my information is used?

1. You can stop being part of the study at any time, without given reason, but we will keep some information about you that we already have.
2. We need to manage your records in specific ways for the research to be reliable. This means we won't be able to let you see or change the data we gold about you.

Will my taking part in this study be kept confidential?
All information which is collected about you during the course of the research will be kept strictly confidential. Any information about you which leaves the hospital/surgery will have your name and address removed so that you cannot be recognised from it.

Research data stored in paper form, such as your age, weight, height, address and medical information, will be stored in a locked filing cabinet in the principal researcher's office. You will be assigned a unique study ID, and experimental data will be stored using this unique ID number on a password-protected computer for analysis purposes. Data will only be accessed by the principal investigator or research team members. Blood samples will be stored in the Human Performance Laboratory freezers at The Royal Wolverhampton Hospitals NHS Trust, New Cross Hospital, Wolverhampton WV10 0QP. In line with the University's guidelines on records management, research data will be retained intact for the study period. Should you withdraw from the study, your personal information (i.e., name and contact details) will be destroyed. However, your research data up until the point of withdrawal (i.e., results from blood samples) will still be included in our research findings. The result of the study is expected to be published in a scientific journal, but your name will never be published. All data will remain completely confidential at all times.

Where can I find out more about how my information is used?
You can find out more about how we use your information:

- At www.hra.nhs.uk/information-about-patients/
- Leaflet available at www.hra.nhs.uk/patientdataandresearch
- By asking one of the research team,
- By sending an email to the study PhD student Hazel Shanley (h.a.shanley@wlv.ac.uk), or
- By contacting the Study Sponsor's Data Protection Officer, Dr Hilary Paniagua (h.paniagua@wlv.ac.uk or 01902518639).

What will happen to the results of the research study?
The results will be written up into a PhD thesis and may be used for publication within approximately 1-2 years of the study, as well as for presentations and conferences. Participants of this study will not be identifiable in any reports or publications. You can obtain a copy of the results by contacting the research team at the University of Wolverhampton (h.a.shanley@wlv.ac.uk). You will not be identified in any report or publication.

Who is organising and funding the research?
The research is organised and funded by the University of Wolverhampton University as part of a PhD in the Faculty of Education, Health, and Wellbeing. Approval for this study has been granted by the University of Wolverhampton, the Department of Sport Ethics Committee, the Health Research Authority Ethics Committee and the Royal Wolverhampton Hospitals NHS Trust Research and Development Ethics Committee.

Who has reviewed the study?
This study has been reviewed in the standard manner by the research supervisors, the sponsor (the University of Wolverhampton) and the Royal Wolverhampton Hospitals NHS Trust research and development.

How can I withdraw from the study?
The research you will participate in will be most valuable if few people withdraw from it, so please discuss any concerns you might have with the investigators. During the study itself, if you do decide that you do not wish to take any further part, then please inform one of the research team as soon as possible, and they will facilitate your withdrawal. Any personal information or data you have provided (in paper or electronic form) will be destroyed/deleted as soon as possible. However, your research data up until the point of withdrawal (i.e., results from blood samples) will still be included in our research findings. After you have completed the research, you can still withdraw your personal information by contacting one of the research team (their contact details are provided on this form; give them your participant number, or if you have lost this, give them your name). If, for any reason, you wish to withdraw your research data, please contact the investigator within a month of your participation. After this date, withdrawing your individual data may not be possible as the results may already have been published. However, as all data are anonymised, your personal data will not be identifiable in any way.

If a participant loses the capacity to consent, they will be withdrawn from the study by the study investigators. Identifiable data and samples already collected will be kept.

General data protection regulation statement

Data will be protected following the Data Protection Act (2018). All data will be maintained as confidential and anonymous until securely destroyed.

Contact for Further Information
If you have any problems or questions relating to the study, please contact Hazel Shanley (h.a.shanley@wlv.ac.uk).

Thank you for taking the time to read this information. If you are happy to participate, please sign the enclosed consent form. You will be given a copy of the information sheet and signed consent form to keep.