Imaging of tumour microvasculature using high resolution contrast enhanced ultrasound (CEUS) together with markers of proliferation/ angiogenesis/ vascular mimicry to characterise response to neoadjuvant chemotherapy in triple negative breast cancer.

We invite you to take part in a research study

- 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 such as your friends and family 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.
- Thank you for reading this.

How to contact us:

If you have any questions about this study, please contact **Mr Jaideep Rait** during working hours on the following contact number or email address:

Tel: 01622 939736 (x39736)

Email: j.rait@nhs.net

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1. What is the purpose of this study?

Around 50,000 people per year are told that they have breast cancer in the UK. Triple negative breast cancer (TNBC) is a specific type of breast cancer that is not hormone (oestrogen and progesterone) dependant and accounts for up to 15% of these cases. Treatment for TNBC almost always includes chemotherapy, often given before surgery to try and shrink the tumour.

It can be difficult to track how the cancer is responding to chemotherapy using routine tests such as standard ultrasound or breast MRI. New high resolution ultrasound technology using tiny injected bubbles (microbubbles) holds the promise of improved monitoring by allowing the blood vessels inside the tumour to be seen. Combining this with evaluation of microscopic changes in the tumour will give an insight into how tumour blood flow changes during chemotherapy. Early changes in the blood flow after chemotherapy starts may be a good indicator of whether the cancer will shrink or not. It may even be able to predict those cancers that will shrink away completely or or even whether the cancer will keep growing despite the treatment.

The research is part of Mr Rait's Masters degree at The University of Kent. Mr Rait is a trainee Breast Surgeon (registrar) supervised by the Consultant Breast Surgeon Miss Karina Cox, Consultant Oncologist Dr Catherine Harper-Wynne and Consultant Pathologist Dr Sonia Saw as well as Professor Michelle Garrett at the University of Kent and Professor Mengxing Tang at Imperial College London.

If successful, this research will lay the foundation for a larger study to see if the new technology can replace the existing standard imaging tests used to diagnose and monitor TNBC during chemotherapy.

2. Why am I being chosen?

We have chosen to approach you to take part in the study because you have recently been diagnosed with triple negative breast cancer (TNBC). As part of your treatment, your specialists have recommended that you have chemotherapy first followed by surgery.

3. 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 not affect the standard of care you receive. It is also important that you are not taking part in any other research studies while you are involved with this study. Your involvement with this study ends after you have surgery.

4. What will happen to me if I take part?

Your breast cancer treatment will happen normally. The only difference will be that you will be monitored more closely during chemotherapy with the high-resolution contrast test and 2 extra biopsies will be taken from the cancer. We need to take the extra biopsies to see whether the ultrasound blood flow changes accurately reflect what is happening at the microscopic level inside the tumour. Your GP will be informed of your involvement in the study unless you instruct us not to do so.

- If you agree to take part, you will need to come back for **three** extra visits to your breast unit's ultrasound department to have the new high-resolution contrast ultrasound test and extra biopsy samples taken will be taken on **two** of those visits. These visits will take place: **(1)** before starting chemotherapy (ultrasound and biopsy), **(2)** between your 2nd and 3rd dose of chemotherapy (ultrasound and biopsy) so we can assess what happens in the first few weeks after starting chemotherapy and **(3)** 2 weeks after chemotherapy finishes (ultrasound only).
- A member of the research team will insert a cannula (small tube) into a vein in your arm before the test and inject the ultrasound contrast.
- A consultant breast radiologist will perform the new ultrasound test with a member of the research team and a biomedical engineer from Imperial College also present for the procedure.
- The research test should take about 45 minutes.
- After the images are obtained, on visits **(1)** and **(2)** local anaesthetic will be injected, and a biopsy of the tumor taken. On visit **(1)**, some of the tissue will be transported to UCL genomics in London to see if the tumour is carrying genetic mutations in the breast cancer linked genes BRCA1, BRCA2, CHEK2 and PALB2. The rest of the tissue and all the biopsy sample on visit **(2)** will be sent firstly to the hospital's pathology department for processing and then transported to the School of Biosciences at the University of Kent for the research tests to be performed as soon as they arrive. After the research tests have been completed, the biopsy material will be disposed of in accordance with the UK Human Tissue Act.
- After the test, you will be asked to complete a satisfaction questionnaire by a member of the research team. You can complete this before going home or take it home and post it back to the research team.
- Following these three visits and after finishing chemotherapy you will have your breast surgery as normal standard of care.

5. What do I have to do?

Before and after the new ultrasound test, you can behave normally and take regular medications. It is fine to drive yourself or use public transport to get to the appointment, but you may prefer to have someone with you. We can offer you reasonable travel expenses or a waiver for your parking costs.

6. What is the drug and intervention that is being tested?

The drug is called SonoVue and it is a microbubble ultrasound contrast agent. Microbubbles are tiny gas filled bubbles that are smaller than a red blood cell. The bubbles reflect the ultrasound beam to show structures in the body. The hexafluoride gas in the microbubbles is quickly and harmlessly removed from the body by the lungs. They have been used for many years to look at blood flow in arteries and internal organs by injecting them into the bloodstream.

This research uses SonoVue microbubbles injected into the bloodstream (up to 5ml). People with serious heart, lung or kidney disease should not have microbubbles injected into the body. Likewise, people who have recently had a thromboembolism (major blood-clot) or whose blood is prone to clotting (hyper-coagulation disorder) should not have injected microbubbles.

The equipment being used to develop the new ultrasound test is made up of a research ultrasound machine, which is safe to use in studies on people. This machine will be attached to a normal ultrasound probe (already in use on patients) and this lightweight probe is the only part of the equipment that will be in contact with your skin. An experienced radiology doctor will perform the test ultrasound scan.

The extra biopsies for the research are taken in the same way as the biopsy you had when your breast cancer was first diagnosed.

7. What are the side effects of the biopsy and having the new ultrasound test?

Injecting SonoVue microbubbles into the bloodstream is safe but there are some uncommon (1/1000 to 1/100) side-effects that could occur immediately after the injection such as headache, dizziness, tingling of the skin, a funny taste in the mouth, skin flushing, sickness, abdominal pain, skin rash, discomfort in your chest, feeling hot and skin redness at the site of the injection. Rare (1/10,000 to 1/1000) side effects include allergic reaction, blurred vision, low blood pressure, itching of the skin, back pain, chest pain and fatigue.

There are no known long-term side effects of SonoVue microbubbles.

Possible side effects of the biopsy include blood collection (haematoma), bruising and soreness.

8. What are the possible disadvantages and risks of taking part?

You will need to come back to the breast unit for three extra visits, which may be inconvenient.

9. What are the possible benefits of taking part?

We cannot promise the study will help you but the information we get might help improve the treatment of people with triple negative breast cancer in the future.

You will be monitored more closely than normal as you go through the chemotherapy. The new ultrasound test uses cutting edge technology called 'high-resolution contrast enhanced ultrasound' that is much more powerful than a normal ultrasound. It is therefore possible that during the research test, when the radiology doctor scans your breast they may find the breast tumour is bigger than initially measured or there is more than one cancerous area in the breast. If this happens, this information will be given immediately to the doctors involved in your care as it may affect your treatment plan. They will then organise another appointment with you to talk about the findings. Additionally, the information gained from the biopsy samples as well as the new ultrasound test may show that there has been a greater or lesser response to the chemotherapy than expected and this information will be relayed immediately to the doctors involved in your care.

We are also planning to see if the cancer has mutations in the BRCA1/2 genes and this information will be given to your oncology doctor as it may change the type of chemotherapy that they give you. If the cancer comes back in the future, either as a recurrence in the breast or armpit or as secondary breast cancer, knowing whether the original cancer was carrying mutations in the BRCA1/2 genes, could affect the type of treatment offered to you by your doctors.

Sometimes during the course of a research project, new information becomes available about the intervention/ drug that is being studied. If this happens, your research doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw, your research doctor will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form.

10. What happens when the research study stops?

After the extra visits for biopsy samples and high-resolution ultrasound your breast cancer treatment will carry on as normal. This means that when the research study stops, your ongoing treatment and care will not be affected.

11. What if something goes wrong?

Maidstone and Tunbridge Wells NHS Trust holds standard NHS Hospital Indemnity and insurance cover with NHS resolution for NHS Trusts in England, which apply to this study. This does not affect your legal rights to seek compensation. If you are harmed due to someone's negligence, then you may have grounds for a legal action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during the course of this study then you should immediately inform the research team. The normal National Health Service complaints mechanisms are also available to you.

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be fully addressed. If you have a concern about any aspect of this study,

you should ask to speak with the doctors or chief investigator (Miss Karina Cox, karina.cox@nhs.net), who will do their best to answer your questions. If you are still unhappy and wish to complain formally, you can contact the Patient Advisory Liaison Service (PALS):

Telephone: 01892 638237/632953

By email: mtw-tr.palsoffice@nhs.net

12. How will we use information about you?

Maidstone and Tunbridge Wells NHS Trust are the sponsors for this study. Maidstone and Tunbridge Wells NHS Trust will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. Maidstone and Tunbridge Wells NHS Trust will keep your personal data for:

- 10 years after the study has finished in relation to data subject consent forms.
- 10 years after the study has completed in relation to primary research data.

Certain members of the research team will need to use information from your medical records for this research project. This information will include your initials, NHS number, name, date of birth (which will be used to calculate age), and contact details. Other members of the research team who do not need to know these details will not be able to see your name or contact details and your data will have a specific 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 keeps your identity secure and prevents others from knowing that you took part in the reasearch.

Legal basis

As an NHS Hospital Trust, we use personally-identifiable information to conduct research to improve health, care and services. As a publicly-funded organisation, we have to ensure that it is in the public interest when we use personally-identifiable information from people who have agreed to take part in research. This means that when you agree to take part in a research study, we will use your data in the ways needed to conduct and analyse the research study.

Health and care research should serve the public interest, which means that we have to demonstrate that our research serves the interests of society as a whole. We do this by following the UK Policy Framework for Health and Social Care Research.

International transfers

There may be a requirement to transfer information to countries outside the UK and European Economic Area (for example, to a research partner). Where this information contains your personal data, Maidstone & Tunbridge Wells NHS Trust will ensure that it is transferred in accordance with data protection legislation. If the data is transferred to a country which is not subject to a European Commission (**EC**) adequacy decision in respect of its data protection standards, Maidstone & Tunbridge Wells NHS Trust will enter into a data sharing agreement with the recipient organisation that incorporates UK/ EC approved standard contractual clauses that safeguard how your personal data is processed.

Sharing your information with others

For the purposes referred to in this privacy notice and relying on the bases for processing as set out above, we will share your personal data with certain third parties.

- Other NHS Trust employees, agents, contractors and service providers (for example, suppliers of printing and mailing services, email communication services or web services, or suppliers who help us carry out any of the activities described above). During the study, all hard copy documents containing participants identifiable data (e.g. consent forms) will be stored in locked filing cabinets within alarmed, access restricted hospital buildings. Only the study team will have access to these locked cabinets. Electronic data will only be accessible via a password protected database held on a secure server. Our third party service providers are required to enter into data processing agreements with us. We only permit them to process your personal data for specified purposes and in accordance with our policies.

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. 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.

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

You can find out more about how we use your information

- at www.hra.nhs.uk/information-about-patients/
- by asking one of the research team
- by sending an email to Miss Karina Cox (karina.cox@nhs.net).

Complaint

If you wish to raise a complaint on how we have handled your personal data, you can contact Maidstone and Tunbridge Wells NHS Trust Data Protection Officer (XXXXXX) who will investigate the matter. If you are not satisfied with our response or believe we are processing your personal data in a way that is not lawful you can complain to the Information

Commissioner's Office (ICO) by visiting **https://ico.org.uk/make-a-complaint/** or by calling their helpline on 0303 1231113.

13. What will happen to the results of the research study?

The results of the study will be presented at bio-medical engineering and medical meetings and be published in bio-medical/ medical journals. You will also be sent a report of the study (with a link to the medical journal) using words that can be easily understood by people who do not have a background in medicine or science. You will not be identified in any report/ publication.

14. Who is organising and funding the research?

The research is being funded by Breast Cancer Kent and Maidstone & Tunbridge Wells NHS Trust. A research team composed of biomedical engineers at Imperial College London, breast cancer doctors at Maidstone and Tunbridge Wells NHS Trust and Cancer biologists at The University of Kent have organized the research.

The doctor conducting the research is not being paid to include you in the study.

15. Who has reviewed the study?

The XXXX Research Ethics Committee have reviewed this study and have given ethical approval.

Thank you for taking time to read this and for considering taking part in this study.