The ZOLMENO study

Why does the effect of zoledronate on breast cancer depend on menopausal status?

We invite you to take part in the ZOLMENO study

Before you decide whether or not to accept this invitation it is important for you to understand why the research is being done and what it would involve for you.

Take time to read the following information carefully and discuss it with others if you wish. Please ask us if anything is not clear or if you would like more information.

You are free to decide whether or not to take part in this research study. If you choose not to take part this will not affect your care.

Thank you for reading this information sheet. If you decide to take part in the ZOLMENO study you will be given a copy of your signed consent form to keep with this information sheet.

Important things you need to know

- We want to find out why a drug given to improve bone health (Zoledronate which belongs to a class of drugs called bisphosphonates) reduces the chance of breast cancer coming back and spreading to the bones for some patients.
- We are studying the changes caused by Zoledronate in blood, cancer cells and bone and how this differs depending on whether you have been through menopause or not.
- This research will help us to understand why some patients benefit and why others don't so that, in the future:
  - We can give Zoledronate to the patients who are most likely to benefit from the drug
  - We can identify other ways of improving treatment in those who are less likely to benefit.
- The study will involve giving a single dose of Zoledronate to all those taking part.
- Taking part in the study will mean 3 or 4 extra clinic visits with blood tests and having a bone marrow sample taken at the time of surgery (when you are already under a general anaesthetic).
- You can stop taking part in the study at any time without giving a reason.

Contents

How to contact us

If you have any questions about this study please talk to your study doctor or research nurse.

Contact for Research Team:

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Lead Research Team:

Professor Janet Brown, Chief Investigator

Dr Elisavet Theodoulou, Study Doctor

1 Why are we doing this study?

Breast cancer is the most common type of cancer in the UK, with 1 in 8 women developing it in their lifetime. Thankfully 8 out of 10 of these women are still free from their breast cancer ten years after treatment.

Recent research has shown that if women with early breast cancer are given a type of drug called a *bisphosphonate* then the cancer is less likely to spread to their bones and they are more likely to live longer. But this benefit was only seen in women who had already been through the menopause (post-menopausal women).

Bisphosphonates are a type of drug normally given to make bones stronger and some women already receive these drugs as part of their breast cancer treatment.

Bisphosphonates seem to work against cancer cells in the bones of post-menopausal women, but we don't know exactly how or why. After menopause a woman's hormone levels change and we think that it is these different hormone levels which allow the bisphosphonate to work better than in women who have not been through the menopause.

Through the ZOLMENO study we plan to show exactly how and why Zoledronate (a bisphosphonate) works to reduce the chance of cancer spreading to bone in post-menopausal women. We hope it will then be possible to identify which women will get most benefit from being given Zoledronate and then to develop different treatments which are more likely to benefit pre-menopausal and menopausal women.

2 Why am I being asked to take part?

You are being asked to participate in this research because you have been diagnosed with early breast cancer and your initial treatment is going to be surgery to remove the tumour. We need to recruit 40 pre-menopausal women and 40 post-menopausal women to take part in the study to have enough data to find out why bisphosphonates make a difference in some women but not others.

It is your decision whether to join the study or not. We will describe the study to you and go through this information sheet. After considering the information, if you agree to take part, we will then ask you to sign a consent form. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive.

3 What will happen to me if I take part?

Study visits

We will ask you to make 3-4 extra visits to study clinics. Wherever possible the study visit will be combined with your routine appointments but it is likely that at least 2 of these will be on different days. We can offer payment for all or part of your travel costs for these study visits.

Study treatment

Women taking part in this study will be split into two groups. Everybody taking part will be given a single dose of Zoledronate, with Group A having it 1 week before surgery and Group B having it 3 weeks after surgery. Zoledronate is given through a thin plastic tube (cannula) into a vein in your arm or the back of your hand. It will be given at Weston Park Hospital and takes 15 minutes to give. We will take one of your research blood tests at the same time as we place the cannula in the vein so this will not involve an extra needle. Zoledronate is commonly given to cancer patients and we are using the same dose that is used in these situations. This is explained in more detail below.

Study blood tests

You will have some blood taken (about 15ml or 3 teaspoons) to check you are suitable for the study (screening tests). These will be combined with tests you would have as part of your normal care wherever possible (so will not always be extra tests or extra needles).

If the screening tests confirm that you are able to enter the study then you will have blood tests on several occasions during the study period so that we can measure the effect that your surgery and

the Zoledronate have on the hormone levels we are investigating. The amount of blood taken will be up to 40ml (8 teaspoons). Again, we will combine these with routine tests you are having wherever possible but it is likely that at least two of the blood tests will involve an extra blood test.

Study bone marrow tests

At the same time as your surgery (when you are already asleep under the general anaesthetic), we will take a bone marrow sample from the back of your hip bone. This is above the buttock, well away from your spine and hip joint. The bone marrow sample is taken using a special needle that is less than 2mm wide. A syringe is used to remove some of the bone marrow cells (less than 5ml or a teaspoon full), which looks like a thick blood sample. A slightly wider needle (3mm) is then inserted in the same place to take a small core of the bone marrow (this looks like red spongy tissue). This is a very quick procedure and will not affect the surgery that you have or your recovery afterwards. This procedure will be performed by a research doctor who is experienced in this procedure.

It would be very helpful if we could have an additional bone marrow sample from each patient either before or after Zoledronate treatment, so that we can compare changes caused by the treatment. However this is not something that you have to agree to in order to take part in the study. This is a common procedure routinely done under local anaesthetic (a numbing injection) in many cancer patients but because some people do experience discomfort during the procedure we are asking if you would be willing to have this done as an *optional* part of the study.

How is this different from normal care?

Current national (NICE) guidelines recommend the use of bisphosphonates in breast cancer patients who have had or are having cancer treatment which is likely to thin their bones or in patients whose cancer has already spread to their bones.

In this study, you will receive a single dose of a bisphosphonate (Zoledronate) through your vein and this will be additional to any bisphosphonates you may receive in your standard care, alongside your other cancer treatment.

Who decides which group I would be in?

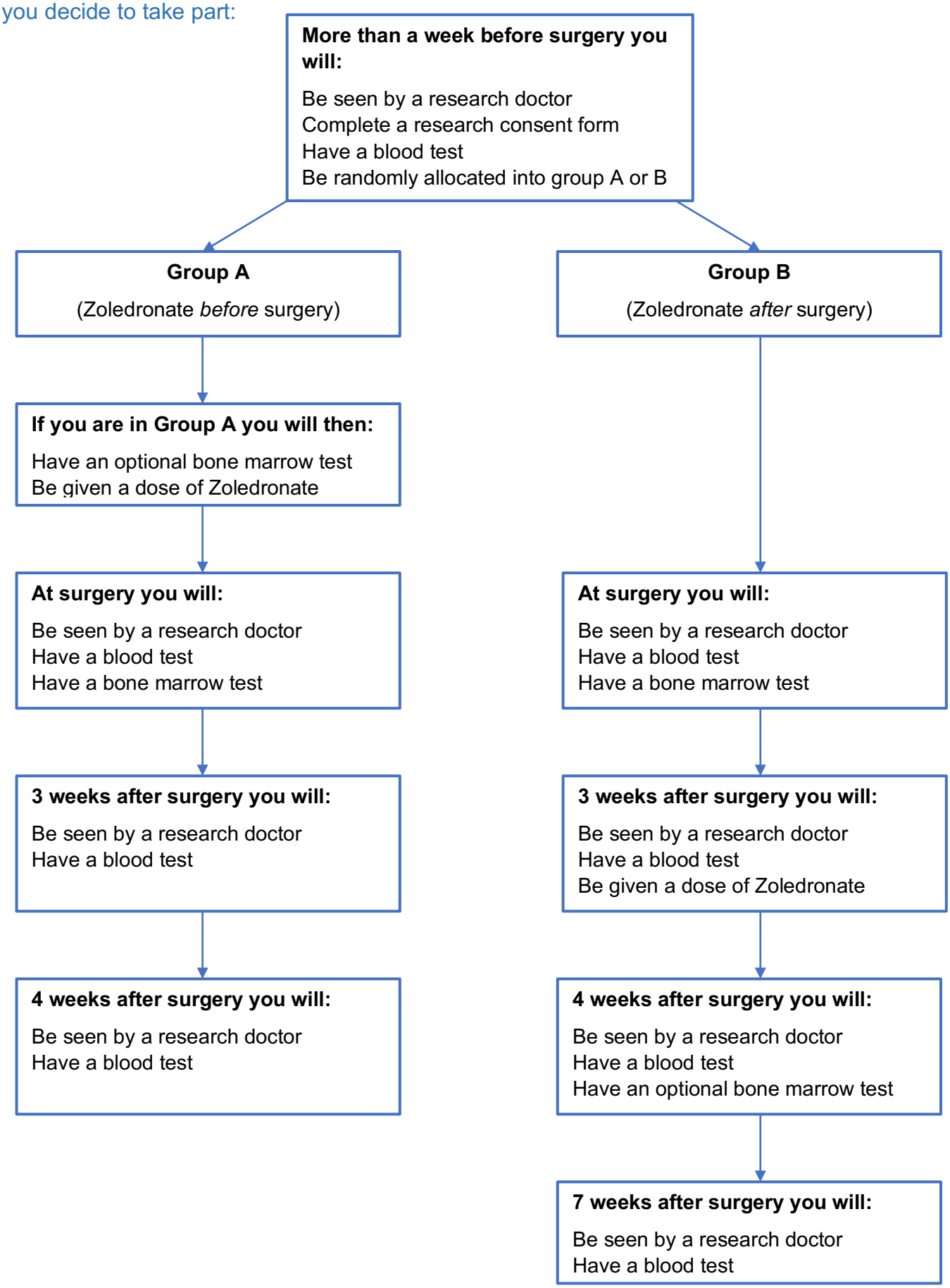
The best way of finding out how Zoledronate affects breast cancer and the bones of breast cancer patients, as well as how this differs depending on whether you have been through menopause or not, is to put patients into groups and give each group treatment at a different time – one group when the tumour is still in the body, and one group when it has been removed. There is nothing to suggest that this makes a difference to the benefit people would have from the treatment but it will help us figure out how and why bisphosphonates benefit some patients and not others. To try to make sure the groups are the same to start with each patient is put into a group by chance (randomly). This is called a randomised study. A computer programme will select randomly whether you have the Zoledronate before or after your surgery. You, your doctors and your nurse will not be able to choose which group you are in. You have a 50% chance of being in either group. All patients will receive Zoledronate and no placebo treatments will be given.

How will the effect of the treatment be tested?

The effect that Zoledronate has on your bone and the breast cancer itself will be measured through the blood tests and bone marrow samples taken at the times shown in the diagram below. This will include blood tests before the treatment and after the treatment and your surgery. In addition, when the hospital has finished testing the cancer that is removed from your breast, they will give us a small part for us to also run tests on.

It is unlikely that you will experience any problems from the treatment you receive or from the bone marrow procedure, but we will monitor you for any side effects when we see you at the study visits after your bisphosphonate treatment and bone marrow samples. You will also be encouraged to contact the research team if you experience any problems between study visits (contact details at the front and back of this document).

If you decide to take part:



How long will I be part of the study for?

Your active involvement in the study will be from the point you decide to take part to 4 weeks after you have received the Zoledronate treatment. If, at any time, you decide you no longer wish to take part in the study your involvement will stop immediately. We do not expect you to have any ongoing problems from involvement in the study, but if this does occur we would follow you up over a longer period of time, alongside your normal doctors.

In addition to the tests done during the study, the samples of blood, cancer cells and bone marrow that you give us as part of the study will be stored and used in research for a longer period after you have left the study. Your samples will also be stored anonymously, and used for related medical research which we hope will help even more breast cancer patients in the future.

4 What are the possible risks of the study?

Risks related to the treatment

All drugs or medicines carry the possible risk of unwanted side effects. Zoledronate is a commonly used bisphosphonate drug, which many people are given without experiencing any problems. Problems that can occur with Zoledronate are often after many or frequent doses of the drug. As you would be receiving just one dose of the drug the risk of side effects is much reduced.

One risk to be aware of which can affect from 1 in 10 up to 1 in 100 patients is flu-like symptoms within the first 3 days after the dose is given. This can include some of the following symptoms, but is very unlikely to include all of them:

- raised temperature
- bone, joint or muscle aches
- headache
- sore or itchy eyes
- stomach upset such as feeling or being sick, or diarrhoea (loose stools)

These symptoms, if experienced, usually settle down within 24 hours. We recommend that you take paracetamol, and/or something like ibuprofen, to relieve the symptoms if they occur.

Another possible risk is an effect on the levels of salts in your blood or your kidney function. However, this is very unlikely as we check your blood tests before giving the Zoledronate and we would not allow you to take part in the study if there were already any problem with your kidneys. As an extra safety check we will also monitor the function of your kidneys with the study blood tests taken one week after the drug is given. In the unlikely event that a problem occurred we would treat you with some fluids given through a vein.

A rare side effect that is very unlikely with a single dose of zoledronic acid, but something you should be aware of, is a problem called ‘osteonecrosis of the jaw’. This is damage to the jawbone and is more likely if you have dental problems. It is very rarely seen with a single dose of Zoledronate but to reduce the risk we would not allow you to take part in the study if you have had recent dental extraction or jaw surgery, as assessed by the investigators.

Risks related to the tests

Some people may find the insertion of the needle used to take blood and access the vein to give the Zoledronate briefly painful or uncomfortable. Otherwise these are very safe procedures with a very low risk of unwanted side effect.

Having a bone marrow sample taken is also considered to be a safe procedure. It can be associated with discomfort or short lived (a few seconds of) pain but this will be avoided by performing the procedure why you are asleep under the general anaesthetic for your surgery. It is very unlikely that you will feel any discomfort in the area after the surgery. If you did feel any discomfort such as mild bruising is very likely to have gone within 24 hours and will be improved with simple painkillers such as paracetamol, which you are likely be taking post-surgery anyway.

If you agree to having an extra bone marrow sample taken for the study, in addition to the one taken at surgery, this would be done while you were awake, at one of the clinic visits. The numbing injection (local anaesthetic) used can sting for a

few seconds. If you have had a biopsy taken from your breast cancer it is the same type of injection used. Then you would feel some pressure as the needle was inserted into the bone marrow. Most people don't feel pain as the sample is taken, but some feel a discomfort or sharpness for a few seconds.

The risks of bleeding or infection from this procedure are extremely rare, but we advise patients to leave the small plaster/dressing on for a day or so to protect the area.

Pregnancy and breastfeeding

There is not enough information available from patients being given Zoledronate when they are pregnant or breastfeeding to tell us whether it causes harm to unborn and young babies. We would therefore not allow you to take part in the study if you were pregnant or breastfeeding. You would need to use a reliable form of effective contraception during the study, including for the 4 weeks after receiving the Zoledronate. This will also be important as part of your ongoing cancer treatment.

5 What are the possible benefits and disadvantages of taking part?

This study will allow us to identify how and why Zoledronate reduces the chance of breast cancer coming back or spreading in some women and not others. We hope that the results of this study will help us to develop and deliver effective treatment to many women like you in the future. Taking part in this study will involve attending between 2 and 4 extra clinic visits, including the treatment and tests described above. We will repay you for your travel expenses to these clinics but you should consider whether you are able to commit to the extra time and tests involved.

Bisphosphonates (including Zoledronate) are given to patients because they are very good at improving and protecting bone strength. The benefit of a single dose of Zoledronate will gradually fade but can continue for up to 2 years. This is an important consideration for patients with breast cancer as chemotherapy and hormone treatments can have the unwanted side effect of thinning the bone, increasing the risk of brittle bones and breaks or fractures in the future. Therefore by taking part in this study we would expect you to have some benefit in bone strength from this treatment, although because we will not measure this we cannot guarantee this benefit.

Whether you decide to participate in the study or not will not impact on your future treatment; should you need to be given bisphosphonates as part of your ongoing treatment this will occur regardless of whether you have taken part in this study.

Pre-menopausal and menopausal women

A study of over 18,000 women with early breast cancer who were treated with bisphosphonates for 5 years showed that these drugs reduced the chance of cancer spreading or coming back in women who had been through the menopause more than five years previously. It did not make things any better or worse for women who were pre-menopausal or going through the menopause. So although the study may not help your cancer treatment directly, the information we get from this study will help improve the treatment of people with early breast cancer in the future, including helping us to work out ways to improve treatment of pre-menopausal and menopausal women such as yourself.

Post-menopausal women

The study described in the paragraph above suggests that you may have some anti-cancer benefit from receiving a bisphosphonate as part of your cancer treatment. This would include the dose of zoledronic acid given as part of this study, but generally we think women need longer-term treatment for full benefit. This is likely to be given to you as part of your ongoing cancer treatment after your surgery.

6 What happens when the study ends?

At the end of the study you will continue with any ongoing cancer treatment that has been arranged by your oncologists (cancer doctors) and surgeons. This will not have been affected by you taking part

in the study. If you have experienced any unexpected problems relating to the study we will continue to see you as required.

If the study needs to stop sooner than expected we will explain to you why this has happened.

We plan to publish the results of the ZOLMENO study in a medical journal so that the wider medical community and patients can benefit from the findings. It will not be possible to identify individual patients in any publications or results that we share. If you would like to receive a copy of the published results please ask one of the research team.

We will use the data and samples collected as part of this study to help us carry out further research in the same area of medicine. This means that your involvement in the ZOLMENO study could have even greater benefit for future breast cancer patients.

7 What if I have concerns?

We will make every effort to give you the very best care during this research study. However, if you need to make a complaint about any aspect of your involvement in the ZOLMENO study you can do so by contacting Professor Janet Brown in the first instance. You can also contact the Patient Services Team, Monday to Friday 9am till 5pm by telephone on 0114 271 2400, via email on PST@sth.nhs.uk or in person in the Patient Partnership Department on B Floor, Royal Hallamshire Hospital.

In the unlikely event that you feel you have been harmed in some way as a result of your involvement in this research, you may be able to seek compensation. This would not include action against any of the already recognised possible side effects of the drug or tests done as part of the study. Compensation claims would only be valid where negligence has occurred via the usual mechanisms for claims against the NHS and you would be responsible for any associated legal costs.

If you have private medical insurance you should advise your insurer that you are taking part in research. They will tell you if it would affect your policy with them.

8 What happens to information about me?

All of the information that we collect about you during the ZOLMENO study will be handled in line with the consent that you give and the 1998 Data Protection Act and as such it will be kept strictly confidential. It will not be possible to identify you from any reports or publications relating to this research. The only document containing your full name will be the consent form. You will be given one copy of the consent form, another will be kept in your medical records and the final one will be kept in the research site file, which is stored securely at all times. When we check if you are suitable for the study the paperwork will include your initials, hospital number and date of birth. Following on from this you will be allocated a unique study number and paperwork will only document your initials and this study number. All data will be stored securely in paper and/or electronic format at the Clinical Trials Research Unit at Weston Park Hospital.

As part of the study we will analyse your bone marrow samples to see if Zoledronate 'switches on or off' any particular genes in your bone marrow DNA. We will not be analysing your DNA for any genetic risk factors that would affect you or your relatives' care and genetic data will not be shared on an individual basis.

The information collected about you and samples collected from you may be shared with other research teams in the UK and overseas to answer new research questions in the future. All researchers must comply with similar levels of confidentiality and data protection as described above.

9 More information about taking part

What if new information becomes available?

Sometimes during the course of a research project, new information becomes available about the

treatment or drug that is being studied. It is unlikely that this will happen with a drug such as Zoledronate as it has been widely used for a long time, but if this does happen your research doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to leave the study your ongoing care will not be affected. If you decide to continue in the study you may be asked to sign an updated consent form.

Occasionally on receiving new information your research doctor may consider it to be in your best interests to withdraw from this study. They will explain the reasons for this and arrange for your care to continue.

Who is organising and funding the research?

The ZOLMENO study is being organised by the University of Sheffield in collaboration with Sheffield Teaching Hospitals, Weston Park Academic Unit of Clinical Oncology and the Cancer Clinical Trials Centre. The study is funded by a research grant from the charity Yorkshire Cancer Research.

Who has reviewed the study?

To obtain funding from Yorkshire Cancer Research and approval to run at Sheffield Teaching Hospitals this study has been reviewed by medical experts and patient representatives to make sure it is important and relevant to the care of patients with breast cancer in the Sheffield and Yorkshire region, as well as the UK more widely. It has also been reviewed by a national NHS Research Ethics Committee to make sure that every aspect complies with the ethical requirements for clinical research.

Involvement of the General Practitioner (GP)

We would like to tell your GP that you are taking part in the ZOLMENO study, and will ask for your consent to do this. Apart from this, all information about you and your treatment will remain confidential.

Additional research

Breast cancer research is very important, and new important research questions are arising all the time. Because of this we would like to be able to use the samples of blood, cancer and bone marrow collected from you to perform additional research in the future. This may involve sharing samples with other research groups in the UK and overseas. We will ask your permission to do this when you consent to the study and any available samples will be stored in a Human Tissue Authority (HTA) compliant facility. Strict confidentiality will be maintained at all times and your name and individual details will not be stored with your tissue samples (i.e. they will be anonymised).

The future use of your samples would only be for medical research and they would never be sold for profit. Allowing your samples to be used for research is considered a donation of a gift and you would not receive any financial reward for this.

If you have any questions about the future use of your samples please ask a member of the research team for more information.

10 Contact details for further information

If you have any questions about your diagnosis of breast cancer or about clinical research please discuss them with your doctor.

You may also find it helpful to contact **Macmillan Cancer Support**, an independent cancer information charity (freephone **0808 808 00 00**, website **www.macmillan.org.uk**) or the local **Weston Park Cancer Support Centre** who offer a free drop-in service Monday to Friday 9am to 5pm (telephone **0114 2265666**, website **www.cancersupportcentre.co.uk**).

If you would like more information about clinical research, the UK Clinical Research Collaboration produces a booklet '*Understanding Clinical Trials*'. To obtain a copy contact them on telephone **0207 670 5452** or via their website **www.ukcrc.org**.

Thank you for taking the time to consider taking part in this study.