TO BE PRINTED ON
HOSPITAL HEADED PAPER

EPHOS-B

EFFECT OF PERIOPERATIVE ANTI HER-2 THERAPY ON EARLY BREAST CANCER STUDY BIOLOGICAL PHASE

PATIENT INFORMATION SHEET

We are inviting you to take part in a clinical trial called **EPHOS-B**. Part 1 of this information sheet is about this research and what taking part involves. Part 2 gives you further information about how the study is being carried out.

Before deciding whether to take part, please read it carefully and discuss it with other people if you wish. Please ask your hospital doctor or nurse if there is anything you do not understand or if you want more information. Take your time to decide.

This study forms part of the National Cancer Research Network's portfolio of approved studies.
This research is funded by Cancer Research UK.

Pathway B

CANCER RESEARCH UK

Part 1: About the EPHOS-B study

Why am I being invited to take part in the EPHOS-B study?

A sample of tissue taken from your breast has shown that you have breast cancer and you will be having surgery within the next few weeks. The small piece of tumour which was removed to make the diagnosis showed that it contained high levels of a protein called HER2.

What is HER2?

HER2 occurs on the surface of some cells and makes the cells divide and then grow. Breast cancers that have high levels of this protein tend to grow more quickly, and are therefore more likely to come back. This type of breast cancer is called HER2 positive, and affects about 20% of breast cancer patients.

What is the purpose of this study?

Until a few years ago, the risks of breast cancer returning for patients with HER2 positive breast cancer were comparatively high. However, several studies of a drug called trastuzumab showed that this drug, when given to patients who also had chemotherapy treatment, reduced the risk of breast cancer coming back by about a third. However, despite this progress in the treatment of HER2 positive patients, some risk of the breast cancer coming back still exists, and we need to find ways of reducing it further.

Trastuzumab is a type of treatment known as 'anti-HER2 treatment' and this drug is now routinely included in the treatment plan for HER2 positive breast cancer patients following chemotherapy. Standard treatment for HER2 positive breast cancer is usually surgery, followed by chemotherapy treatment, then trastuzumab taken for the duration of 1 year. The EPHOS-B study will test a new way of giving anti HER2 treatment – that is, in some patients the treatment will also be given for around 10-13 days before surgery and again straight after surgery. This will be followed in all patients by the standard treatment which is usually chemotherapy followed by trastuzumab treatment.

It is known that giving one year of trastuzumab to patients with HER2 positive breast cancer reduces their chance of the cancer returning. However, there are some reasons to think that giving trastuzumab just before an operation for breast cancer might further reduce the risk of it returning, and this study is part of a programme to test this idea. In this study, we plan to see if we can identify any changes in your breast cancer after only 10-13 days' treatment with trastuzumab. We also want to see if those changes might be different if we combine this treatment with another drug that treats HER2 positive breast cancer, called lapatinib. To look at this we will need to compare small samples of tissue and blood collected before and after the study drugs have been taken for the first 10-13 days before surgery.

What are the drugs being tested?

The two types of anti-HER2 treatment which are being used in this study are trastuzumab (also known as Herceptin) and lapatinib (known also as Tyverb) and both drugs have been shown to benefit patients with HER2+ breast cancer.

Trastuzumab works by recognising the HER2 protein on the outside surface of a cell and then locking onto it. When trastuzumab locks onto the HER2 protein it causes the tumour to shrink and/or reduces the risk of the cancer returning. Trastuzumab is now widely used in the treatment of women with early breast cancer.

Lapatinib works in a different way to trastuzumab as its small size allows it to enter the cancer cell and block the HER2 protein on the inside, and thus may cause cancer cells to die. Lapatinib has been given to over 20,000 patients in clinical trials at various stages of their disease but has not yet been approved for sale by government authorities. Lapatinib has been used in patients with advanced breast cancer and found to be effective; this includes patients who have already received trastuzumab.

When the EPHOS-B study was developed in 2007 the trial consisted of 3 treatment groups and women taking part in the trial either received standard treatment; lapatinib alone or trastuzumab alone. The design of the study was based on the best evidence about the two treatments that was available at that time. However, new results from ongoing trials of anti-HER2 therapy have now become available. This research suggests that as trastuzumab and lapatinib work in different ways, a combination of the two treatments may be better than treatment with lapatinib alone. Based on this evidence, Cancer Research UK and the West Midlands - Edgbaston Research Ethics Committee have approved a change to the EPHOS-B trial so that patients will now receive either standard treatment, trastuzumab alone, or a combination of lapatinib and trastuzumab.

Over 100 women were recruited to the first part of EPHOS-B and it is planned that the second part will recruit another 150 patients to the new design of the study. Follow up information will continue to be collected from all women who took part in both parts of the trial.

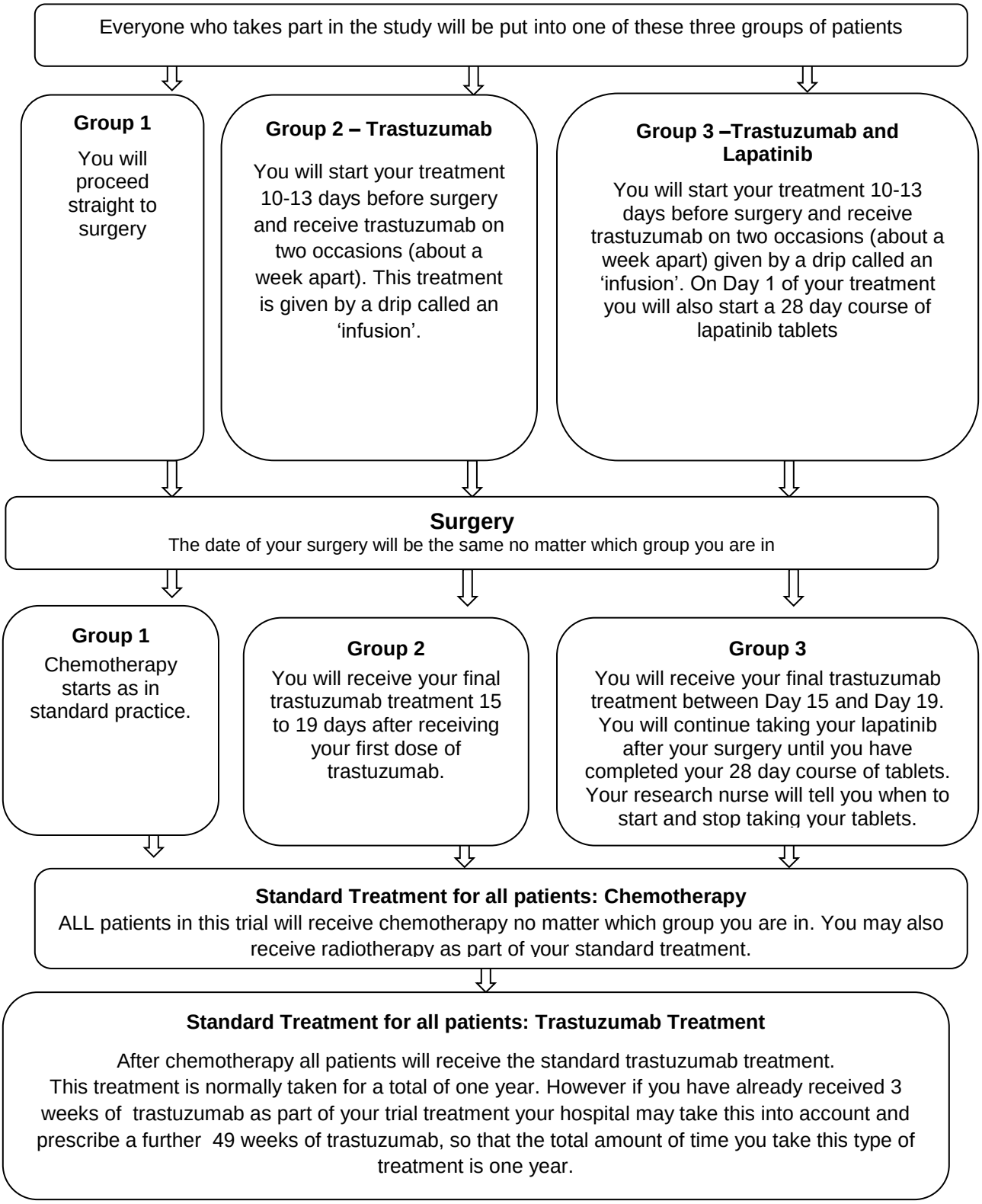
What will happen to me if I take part?

Everyone who agrees to take part in this study will be allocated to one of three groups of patients. The diagram on page 4 will explain about the treatment received by each group. It is important that each group of patients are as similar to each other as possible. This is because we need to be sure that if one group does better than the other group it is because of the treatment and way the treatment was given and not because the patients in the three groups are different from each other in some way. The only way to make sure that the groups are as similar as possible is to allocate patients to a group at random. This process is called 'randomisation'.

Depending on which group you are in the study treatment will last up to 4 weeks. We would like to take blood samples from you when you join the study, when you have your surgery and on one occasion after your surgery.

We would also like to use some of your breast cancer tissue taken away at surgery for this research. This is explained more fully on page 8.

This diagram shows what happens when you join the EPHOS-B study.



What do I have to do?

You will need to have a number of routine examinations before you can enter the study. These include a physical examination and blood tests to ensure your blood counts are normal and that there are no problems with your liver or kidneys. You may also have X-rays and scans to check that your disease has not spread to other parts of the body.

Your hospital doctor will also carry out tests of your heart function so that they can be sure that your heart is working normally. These tests are standard care for anyone receiving anti-HER2 treatment after surgery. These tests are done because earlier studies have shown that some patients taking lapatinib or trastuzumab had reduced heart muscle pumping. Therefore, before you join the study you will have an electrocardiogram (ECG) which is short test to measure the rhythm of your heart beat. You will also have either an ECHO or MUGA test before you join. An echocardiogram (ECHO) is an ultrasound of the heart and a MUGA scan (multiple gated acquisition scan) allows the doctor to look at the way your heart is pumping by injecting a dye into a vein and using a special camera. If you have problems with your heart you will not be able to join this study. The ECG and MUGA or ECHO will be repeated after you have stopped taking the study treatments to make sure your heart function has not been affected.

After you have joined the trial some of the tests will be repeated just before your surgery and again when you visit the hospital for your routine follow up visit about 30 days after surgery. These tests will include blood tests to ensure your blood counts are normal and that there are no problems with your liver or kidneys.

You will also have an examination 6 months after joining the study and again at 12 months, 18 months, 24 months and then annually for another 3 years. You will not be required to make any extra visits to the hospital as part of your follow up in this study or have any extra tests during this time. All the information needed will be sent by your hospital to the central trials office and you do not need to do anything.

What will happen if I am in Group 1?

You will have the standard treatment. Surgery will take place as in routine practice and as planned by your surgeon. You will be given chemotherapy after surgery and then receive trastuzumab for a total of 52 weeks.

What will happen if I am in Group 2: Trastuzumab only?

Your first dose of trastuzumab will be given to you around 10-13 days before surgery. The first day of your trastuzumab treatment is known as Day 1. You will then receive your second dose of trastuzumab about one week later. After surgery you will receive one further dose of trastuzumab 15 to 19 days after you received your first dose. The reason we have allowed some flexibility in the timing of your treatments is to help your research team plan your visits to the hospital.

How will the trastuzumab treatment be given to patients in Group 2?

Trastuzumab is given by a drip (infusion) through a fine tube (cannula) inserted into a vein. It can usually be given in the outpatient department at the hospital. The first dose is given slowly, usually over about 90mins. After this first dose, subsequent treatments normally take about 30 minutes. You will need to stay in hospital for 4-6 hours for the first visit and usually 2 hours for the next two visits, however your hospital doctor will be able to advise you about this. This is to make sure that you are well enough to go home afterwards. When the needle is removed a small dressing or elastoplast will be applied. You will need to make up to 3 extra visits to the hospital to receive this treatment, although you may already be in hospital recovering from your breast surgery at the time of your last treatment (between Day 15 and Day 19).

What happens if I am in Group 3: Trastuzumab and Lapatinib?

You will receive trastuzumab as described for patients in Group 2, starting your treatment 10-13 days before surgery. The first day of your trastuzumab treatment is known as 'Day 1'. We would like you to start taking your lapatinib tablets on Day 1. However to allow some flexibility in your treatment planning you may be able to start your lapatinib treatment either 24 hours before or after Day 1. Your nurse will let you know exactly when you should start and stop taking your tablets including on the day of surgery.

When you join the study you will be given two bottles containing enough lapatinib tablets for you to take 4 tablets a day continuously for 28 days (plus spare tablets). It is important that you take your tablets as instructed. All 4 tablets should be taken at the same time each day in the early evening as one dose, at least one hour before or after a meal.

You should not eat grapefruit or drink grapefruit juice while taking lapatinib tablets as this may interfere with how the tablets are absorbed. You should also avoid taking antacids for one hour before and after taking your tablets.

What happens to the tablets that are left over?

You will be asked to bring the left over tablets with you when you attend the hospital about 30 days after your surgery, so that there is a record of what you have taken.

What are the side effects, possible disadvantages and risks of taking part in the study?

Side effects of lapatinib

Lapatinib is an investigational drug. Like all medicines, lapatinib can cause side effects, though not everybody gets them. Possible known side effects can include tiredness, skin rash appearing on the face, upper arms or chest (like spots with occasional redness), nausea, vomiting, loss of appetite and diarrhoea (which can, in a small number of patients, lead to dehydration. A quarter of patients (1 in 4) who are given lapatinib may be affected by one or more of these side effects. All these side effects disappear when the drug is stopped but they may also get better on their own even when the drug is continued.

A small number of patients (1-2 out of 100) taking lapatinib have experienced clinical signs of some heart damage but many of these patients had previously had other treatments for their cancers. This is why we will check that you have normal heart function before you enter the study.

In very rare cases some minor changes have been seen in the blood tests which look at how the liver is functioning. If severe changes in the blood tests are seen, these may cause symptoms such as itching, yellow eye or skin, dark urine, pain or discomfort in the stomach area. As soon as patients stop taking the tablets the liver tests usually return to normal.

Side effects of trastuzumab

In studies carried out in both cancer patients and healthy volunteers the most common side effects of trastuzumab were fever and chills and, less frequently, pain, weakness, and nausea (feeling sick). A small number of patients have experienced (rare) shortness of breath, low blood pressure, wheezing, constriction of the air passages, fast heart rate, abnormal fluid in the lungs, reduced oxygen in the blood (sometimes requiring help from a breathing machine), breathing difficulties and uncommonly allergic reactions such as hives and swelling in the throat may develop, for which you may need to take an antihistamine.

These events usually happen within 2.5 hours after the start of your treatment or may happen some time after the trastuzumab treatment has been stopped. It is important that you inform your hospital doctor about any side effects you experience.

Most of what we know about the side effects of trastuzumab is from patients who have received this treatment for many months in combination with a particular type of chemotherapy (anthracyclines). Less than 4% of patients (4 in 100) having trastuzumab after chemotherapy have experienced a decrease in heart function and some patients have developed heart failure while having trastuzumab treatment. This is why we will check that you have normal heart function before you enter the study.

In the largest trial undertaken so far using this combination of lapatinib and trastuzumab before surgery, no major cardiac problems were seen in patients and there were no increased side effects associated with taking both drugs, compared to taking lapatinib alone. However, loose bowel motions (i.e. diarrhoea) can occur with both drugs.

Only a limited amount is known of the side effects of lapatinib and trastuzumab. There is no way of predicting if you will experience any, or how severe they will be.

You must contact your hospital doctor if you experience any side effects or if you think that any problems you may have are related to the taking the tablets.

Regarding Pregnancy

If you are pregnant or breastfeeding you should not take part in this trial. This is because the effects of the study drugs on an unborn baby or nursing infant are uncertain. If it is possible that you may become pregnant you may be asked to take a pregnancy test before you enter the study and you will also be asked to use reliable non-hormonal contraception throughout the duration of this study.

Methods include:

- Barrier methods including diaphragm or condom with spermicide

- a coil (an intrauterine device)

It is important you ask your hospital doctor if you want further advice about this. However, if you do become pregnant unexpectedly, please inform your hospital doctor immediately.

Radiation Risks

If a MUGA scan is the method of choice in your centre used to monitor your heart, one scan will expose you to a small controlled amount of radiation. The amount of radiation would be kept to a minimum and there is no risk for the people you come in contact with after the test. The extra radiation dose you would receive per scan would be the equivalent to 2-3 years of natural background radiation. Any amount of radiation that you receive during your diagnosis can add slightly to the risk of developing cancer, but the additional risk from this test will be very small.

What are the potential benefits of taking part?

There is no guarantee that you as an individual will benefit directly from taking part. We hope that the information we gain in the study will benefit patients who develop breast cancer in the future and that you will have helped by taking part.

How will changes in my breast cancer be assessed?

To help us understand the way any changes in your breast cancer may effect future treatments for individuals, we need to compare small samples of tissue collected at the time of diagnosis (i.e. before any trial treatment is given) and then compare the tissue with samples taken at surgery. You have already donated some tissue samples when you had your biopsy and we would like you to donate some more tissue samples when you have your main surgery. Donating samples of breast cancer tissue is an essential part of this research. This should not require any extra hospital visits.

We would also like to take some extra blood samples from you on 3 occasions which are when you enter the study, just before your surgery and about 30 days after your surgery. We will need about 4 teaspoonfuls on each occasion. As far as possible these will be taken at the same time as other routine blood tests.

What will happen to the samples of breast cancer tissue I donate?

The samples of breast cancer tissue you donate will be used for the EPHOS-B study. When you have your breast surgery the rest of the breast cancer will be removed. The samples of tissue you donated will be sent to the Paterson Institute for Cancer Research.

The samples of tissue and blood will be given a unique code number, and stored securely in the laboratory where they will be analysed. The results of the laboratory tests will be coded and linked to the information we collect about your breast cancer and treatment in this study. It will not be reported back to you or your hospital doctor.

The table below shows what samples of blood and breast cancer tissue we would like to ask you to donate:

When we would like you to donate samples	The samples we would like you to donate	How will it affect me?
When you join the study	2 small pieces of breast cancer tissue. OR Tissue already in storage taken when your breast cancer was diagnosed.	You will need to undergo a core biopsy to collect these for use in the EPHOS study OR These will have already been taken and it will not affect you.
	1 extra blood sample for research	As far as possible, this will be taken at the same time as other blood tests.
When you have surgery	2 small pieces of breast cancer tissue	These will be taken during surgery. You will not be aware of it.
	1 extra blood sample for research	As far as possible, this will be taken at the same time as other blood tests before surgery.
Approximately 30 days after surgery.	1 extra blood sample for research	This is an additional test for all patients in the EPHOS- B study.

What are the alternatives to this study?

Participation in this study will not affect the usual standard of care you receive nor will it delay your surgery. If you do not take part in this study you will have your surgery in the normal way, and this may be followed by chemotherapy, radiotherapy and hormone treatment. As part of standard care, patients with HER2 positive breast cancer are usually given trastuzumab every 3 weeks for 52 weeks after surgery and chemotherapy treatment. You will not be offered trastuzumab or lapatinib before your surgery outside of this study.

Do I have to take part?

It is up to you to decide whether or not to take part. If you agree to join then change your mind you can still withdraw without giving a reason. If you withdraw from the study it will not affect the standard of care you receive. It is routine for your GP to be told if you are taking part in this research

What are the benefits and risks of taking part?

There is no guarantee that you as an individual will benefit directly from taking part. We hope that the information we gain in the study will benefit patients who develop breast cancer in the future and that you will have helped by taking part.

What happens when the study treatment stops?

Whichever group you are in, you will have a blood test taken at your first clinic visit 30 days after surgery and an ECG, ECHO or MUGA to test your heart function before you start your chemotherapy. Your hospital doctor will recommend a treatment plan based on your individual needs.

Will my taking part in the study be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in Part 2.

Part 2: General information about how EPHOS-B is conducted

Confidentiality

Your medical notes will be seen by authorised members of the research team at your hospital, so that they can collect information needed for the EPHOS-B study, and also to check that it is correct. When you join the study, your name, date of birth, post code, hospital number and NHS number will be passed to the Institute of Cancer Research Clinical Trials and Statistics Unit where the study is being coordinated. You will be given a unique registration number, which will be used together with your initials and date of birth on forms that the research staff send to the trials office. All information about you will be treated as strictly confidential and nothing that might identify you will be revealed to any third party.

Scientific and medical employees of ICR-CTSU, the University of Manchester and those conducting the study with them, may need to examine your medical records to ensure the study is being run properly and that the information collected on the forms is correct, but your confidentiality will be protected at all times. Your medical notes at the hospital, and study information may also be looked at by GlaxoSmithKline, the pharmaceutical company who manufactures and supplies lapatinib and by national health regulatory authorities who will check the study is being carried out correctly.

In the unlikely event of you having a serious unexpected side effect from any aspect of the study we need to pass the information on to the regulatory authorities.

All samples of tissue and blood you agree to donate will be sent to the Paterson Institute for Cancer Research and identified using your name, date of birth, and a unique trial identification number. This is because samples of tissue/blood from different patients look exactly the same, and it is vitally important we do not get them mixed up. Once your tissue or blood samples arrive at the Paterson Institute for Cancer Research, they will be processed and stored using a sample code. Your name will not be used in the laboratory, and your unique registration number will be used to link information from the laboratory research with other information about your treatment and progress sent by your hospital to the ICR-CTSU.

We will contact your hospital over the years to find out how you are getting on. Ideally we would like to do this for life, but patients often change address and/or GP or lose touch with their hospital. If this happens we would like to use national records which are kept on everyone's health status to find out how you are. One of these is held at the General Register Office (GRO). We will need to give them enough information to identify you. This is usually your name, date of birth, post code and NHS number (or Community Health Index and/or hospital number in Scotland). Any details we receive from any source are confidential and will only be used for the purposes of the EPHOS-B study. Please initial the consent form to show that we have your permission to do this.

Information from your medical records about your treatment and disease will be sent to the Clinical Trials Section at the Institute of Cancer Research. Representatives from that organisation and/or regulatory bodies may wish to see your hospital or clinic records to make sure the information sent was correct. All information will be kept confidential and your name and address will be removed.

Data Sharing

The Sponsors of this study would like to be able to combine information we collect about patients in this study with information collected for other studies, if in the future it is a useful way of advancing our knowledge of the treatment of breast cancer.

We would also like to be able to make your samples and information available to other researchers for future research. Any other additional research using your tissue must be approved by an independent ethics committee before it is allowed to go ahead. Any samples and information transferred to third parties will not contain your personal information, so they will not be able to identify you from the information provided.

If you do not want your breast cancer tissue used for any other future research, you can still enter the study, but you should not initial the consent form giving permission to use your breast cancer tissue for any other future research.

What will happen to the results of the research study?

Independent experts will review the progress of the research, and the results will be published in a respected medical journal once we are sure they are reliable. No information that could identify you will be included and you will not be identified in any report or publication.

We will write the results in lay terms once they are available. Your hospital will be able to give you a copy.

What if something goes wrong?

It is unlikely that anything will go wrong with your treatment or care, but if you wish to complain about any aspect of the way you have been treated during the course of the study you can do so using the normal NHS complaints procedure.

Healthcare professionals working on Clinical Trials are covered by NHS Indemnity and if you are harmed by taking part in this study you may have grounds for a legal action but you may have to pay for it.

In the event that something does go wrong and you are harmed during the research you may have grounds for a legal action for compensation against The University of Manchester and The Institute of Cancer Research but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

The University of Manchester and Institute of Cancer Research have cover for no fault compensation for bodily injury, mental injury or death where the injury resulted from a trial or procedure you received as part of the trial. This would be subject to policy terms and conditions. Any payment would be without legal commitment.

The University Of Manchester and The Institute of Cancer Research would not be bound to pay this compensation where the injury resulted from a drug or procedure outside the trial protocol or if the protocol was not followed.

In the very unlikely event of you experiencing serious side effects from trastuzumab or lapatinib whilst taking part in EPHOS-B, full details would be reviewed carefully by the cancer specialist with overall responsibility for the study. These details will also be sent to the Medicines and Health Care Products Regulatory Agency (MHRA) who oversee the safety of people who take part in any research involving any drug treatment within the UK. We are required by law to do this.

Private Medical Insurance

If you have private medical insurance please check with the company before agreeing to take part that your medical insurance cover will not be affected.

What if I don't want to carry on with the study?

If you change your mind about having the treatment in this study, we would still like to collect information about your breast cancer, and use the samples of tissue you have donated. The information needed is routinely recorded in your medical records and you would not need to do anything. The samples of tissue would be transported, tested and stored, and you need do nothing further. If you do not want this to happen, please tell your hospital doctor or nurse and the samples you have donated will be destroyed.

What if relevant new information becomes available?

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

Who is organising and funding the research?

EPHOS-B is organised by leading cancer specialists at the University of Manchester, University Hospital of South Manchester Foundation Trust, Leeds University and The University of Edinburgh, together with researchers at the Institute of Cancer Research in Sutton, Surrey.

Your hospital doctor will not receive any personal financial payment if you take part.
EPHOS-B has been reviewed and approved by Cancer Research UK who will pay for this research at the Institute of Cancer Research, Surrey and the University Hospital of South Manchester.

The National Health Service Research and Development Executive will pay for the extra nursing and administrative costs incurred by the hospitals. A grant has been received from the manufacturers of lapatinib to cover the costs of checking patients' heart function and the Sponsors will therefore make a payment to the Trust of your hospital for including you in this study. Also, as lapatinib is not routinely available to patients with early breast cancer in the NHS, the company who manufactures this drug has provided a supply of the drug for patients who enter the trial.

Who reviewed this study?

All research carried out in the NHS is reviewed by in independent group of people called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by the West Midlands - Edgbaston Research Ethics Committee on behalf of all hospitals throughout the UK. It has also been reviewed and approved by Cancer Research UK.

What happens now?

Your hospital doctor or nurse will be happy to answer any questions. Once you have reached your decision let your hospital doctor or nurse know. You will be asked to sign a consent form and will be given a copy to keep together with this information sheet.

Further information

Macmillan Cancer support is a registered charity and helps with all the things that people affected by cancer want and need, from specialist health care and information to practical, emotional and financial support (www.macmillan.org.uk).

Breast Cancer Care has a message board on their Internet website where you can read or add messages about deciding to take part and your experiences of treatment. To use it, go to www.breastcancercare.org.uk, select support for you and then click on discussion forums.

You can learn more about clinical trials on the Cancer Research UK's patient website (www.cancerhelp.org.uk).

Thank you for interest in our research.

Your specialist is: *To be added by participating centre*

Contact phone numbers: *To be added by participating centre*