Delete this line, then print first page of Information Sheet and Consent Form on Trust/Hospital headed paper

Bowel cancer patients with a 'BRAF^{V600E}' genetic mutation: - Are 'targeted drugs' better than standard chemotherapy when given before surgery?

PATIENT INFORMATION AND INFORMED CONSENT FORM (PIS)

(A large-print version of this form is available)

We invite you to take part in the international FOxTROT 4 research, part of the FOxTROT research programme. Before you decide, it is important that you know why we are doing the research and what is involved for you.

Why are we doing this research and why should you consider taking part?

You have been diagnosed with stage 2 or stage 3 cancer of the bowel (colon) and your cancer has a particular genetic mutation called BRAF^{V600E}. This genetic mutation can be the main cause for the cancer cells to grow, and current standard treatment options can be less successful in these circumstances. Your surgeon believes your tumour can be removed by an operation but there is always a risk that undetectable cancer cells may remain in your body resulting in your cancer 'returning'.

There are two standard treatment approaches for your bowel cancer:

a) Traditionally, surgery is undertaken to remove the tumour(s) followed by, if necessary, a course of anti-cancer drugs (chemotherapy) to kill off any remaining but undetectable cancer cells.
b) An alternative to this is based on our international FOxTROT 1 research carried out in 2020, which showed that having some chemotherapy **before** surgery (called neoadjuvant chemotherapy), was better for patients.

The FOxTROT 4 research will test whether (or not) taking 2 'targeted' drugs (called encorafenib and cetuximab) **before** surgery is even better for patients with a similar diagnosis to yours than the normal chemotherapy before surgery (as described in b above). A 'targeted' drug is one which targets and attacks specific genes and proteins that help cancer cells survive and grow. These targeted treatments have been shown to be effective for patients with BRAF^{V600E} mutations where their bowel cancer has spread (stage 4 bowel cancer). This research aims to investigate if this treatment is effective for those patients with stage 2 and 3 disease.

To find out more, including what would happen if you decided to take part in this research, please read the following detailed information.

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Part 1 – More detailed information about FOxTROT 4

This document contains a large amount of information and whilst we have tried to make it as complete and understandable as possible, there may be parts which are unclear. Whether you have questions or simply want to check your understanding, we have included a Patient Question Sheet at the back of the document to help you keep note of your queries. You can then raise these matters with our research staff who will be pleased to answer them. Additionally if you would like to read more about FOxTROT 4, further information can be found in the FOxTROT website found at the following link: https://ctru.leeds.ac.uk/foxtrot/for-patients/about-foxtrot-4.

If I take part what will happen?

After we have answered your questions, you will need to complete a 'Consent' form. You will then have the normal pre-treatment tests and some extra ones to make sure this research is suitable for you. You will then receive the targeted drugs called encorafenib and cetuximab. A 'targeted' drug is one which targets and attacks specific genes and proteins that help cancer cells survive and grow.

What is the purpose of this research?

New treatments have to go through a series of clinical trials to test whether they are safe and effective. FOxTROT 4 is classified as phase 2 research where the aim is to make sure the treatment is safe and has some effect on the cancer.

The standard treatment for bowel cancer has been to have surgery to remove the tumour, usually followed by a course of anti-cancer drugs (called chemotherapy). This is to reduce the chance of cancer returning in the future by treating any remaining cancer cells that cannot be seen on scans or by your surgeon.

More recently the international FOxTROT 1 research showed that having some of the chemotherapy **before** surgery (a treatment approach called neoadjuvant chemotherapy) rather than after surgery was safe and reduced the chance of cancer coming back. As a result of the FOxTROT 1 research, this is now a standard treatment option for some bowel cancer patients.

Bowel cancer arises when normal bowel cells become abnormal through developing genetic mutations. Some specific genetic mutations are common in bowel cancer and approximately one in ten bowel cancers will have a mutation in a gene called $BRAF^{V600E}$. For these patients, there is a higher risk of the bowel cancer returning. New drugs can target this mutation. These targeted treatments are a combination of two drugs called encorafenib and cetuximab. Currently these drugs are only used in patients where their cancer has already spread to other parts of the body, where they have been shown to be better than standard traditional chemotherapy.

The FOxTROT 4 trial will test whether the targeted drugs can be given before surgery and if they result in better outcomes for patients with $BRAF^{V600E}$ mutant bowel cancer. We will see if there are differences in:

a) how the tumour has changed in size, comparing an early CT scan (carried out before starting the research treatment) with a CT scan following the drug treatment

b) how the tumour has changed following surgery (using microscopic examination of the tumour after it has been removed)
c) how many patients remain cancer-free 3 years after treatment

If you decide not to take part in FOxTROT 4, your doctor will talk you through the alternative treatment options. Your treatment options and care will not be affected in any way by your decision not to participate in FOxTROT 4.

Description of the treatment

Description of the treatment and any additional tests

Participants will receive two drugs called encorafenib and cetuximab. These drugs are already used as a second standard treatment in patients with BRAF^{V600E} mutant Stage 4 bowel cancer (where the cancer has spread), if they have previously had chemotherapy. Before starting this treatment, you will have an ECG (electrocardiogram or heart tracing). This test is always done before receiving encorafenib.

Participants will have 6 weeks of this treatment **before** their surgery. Cetuximab is given through a 'drip' into the hand (called an intravenous cannula) as an outpatient over 2-4 hours every 2 weeks and encorafenib is taken as capsules once a day for the 6-week period. You will have a second ECG after one month of receiving encorafenib.

After finishing the treatment, you will have a 3 to 4 week rest period, to allow the treatment to have its full effect and for any side effects to settle. You will then have a CT scan so the effect of this treatment on your cancer can be assessed. This CT scan is an additional test that you would not have as part of standard care. Then you will have the surgery to remove the tumour.

Following your operation, you will have a 4 to 8 week recovery period before seeing the oncologist to discuss if further chemotherapy is desirable. When considering what further treatment may be advisable your oncologist will discuss how you got on during the chemotherapy before the surgery and how you have recovered from surgery.

12 weeks of chemotherapy following surgery (known as post-operative chemotherapy) is recommended as part of the FOxTROT 4 research, your oncologist may recommend longer. If you decide that you do not want to have post-operative chemotherapy, or your oncologist doesn't think that it is in your best interests, that is ok. You can still remain part of the research.

Potential Advantages to you

- Participants usually start the anti-cancer treatment shortly after entering the research.
- You will have targeted therapy as part of your cancer treatment before surgery
- Patients that had neoadjuvant treatment before surgery in the FOxTROT 1 study tended to have less complications after the operation which may be the same for FOxTROT 4.
- Previous research has shown that there are fewer serious side effects with the targeted treatment compared to standard chemotherapy.

- Your safety and progress will be carefully monitored throughout the research.
- The satisfaction of knowing that your involvement in this research may help us understand if this is the best treatment for future patients in a similar position to you.

Potential Risks to you

- There are some side effects with taking encorafenib and cetuximab. The most common (more than 10 in every 100 people have one of more of these) are skin reactions, tiredness, feeling weak/sick, diarrhoea and/or constipation, tummy pain, joint/muscle pain, feeling less hungry and being sick. More information on side effects can be found on page 9.
- There is a risk that you may have severe side effects from the treatment that mean that your operation is delayed, or that you may not be fit enough for an operation.
- There is a risk the targeted therapy may not be as effective as chemotherapy when used this way.
- There is a small risk the tumour may continue to grow whilst receiving the treatment before surgery and you may need to have an emergency operation or stent.
- Treatment can have life threatening complications (very small risk) whether given before or after surgery.

Exposure to Ionising Radiation

All CT scans use ionising radiation to form images of your body and to provide your doctor with information about the tumour. We will assess your tumour when you are first diagnosed and later at regular intervals after your surgery including after 3 years. We will look at the results from these scans to help us ensure that you remain disease free and to monitor how colon (bowel) tumours behave.

As part of this research, one additional CT scan, compared with standard care, may be requested by your doctor to reassess the tumour in the period following the treatment before surgery. Ionising radiation from the scan may cause cancer many years or decades after the exposure. The chances of this happening to you as a consequence of taking part in this research are about 0.35% or approximately 1 in 290 cases. For comparison, 1 in 2 people have the risk of developing cancer in their lifetime and a patient with colorectal cancer not taking part in the study would have CT scans leading to a risk of 0.28% or approximately 1 in 360 cases.

Activity Summary Table – research tests

The table below describes the tests and questionnaires you will be asked to undergo and complete as part of this research. Some of these tests would be completed even if you were not taking part in this research. Tests in a shaded box mean that this test is additional to what would usually happen to you in standard care. We will look to organise as many of these activities on the same day (as far as possible) in order to minimise the travel to your local hospital and the impact on your time. We regret that we are unable to cover any additional costs that you may personally incur from participating in this research. Each patient's treatment pathway (journey) is different and these tests may depend on your journey.

Activity	All participants in the research	Before starting neoadjuvant (before surgery) treatment	Before each cycle of neoadjuvant (before surgery) treatment	After neoadjuvant (before surgery) treatment	Before starting chemotherapy after the operation	1 year after you are registered	3 years after you are registered
1. Giving Consent	✓						
2. Providing your medical history	✓						
3. Colonoscopy (test to look at the bowel)	✓						
4. Clinical assessment	✓	✓	✓	✓	✓		
5. Having a pregnancy test (only if you are female and pregnancy is a possibility)	✓						
6. Having a CT scan (chest/abdomen/pelvis)	✓			✓			✓
7. Heart tracing (ECG)		✓	✓ (after 1 month of enrolment)				
8. Having a stored tumour sample sent for MMR testing –see What happens if I decide to take part?	✓						

Activity	All participants in the research	Before starting neoadjuvant (before surgery) treatment	Before each cycle of neoadjuvant (before surgery) treatment	After neoadjuvant (before surgery) treatment	Before starting chemotherapy after the operation	1 year after you are registered	3 years after you are registered
9. Request permission for additional tests on stored tumour sample for future research (optional)	✓						
10. Routine blood tests to make sure it is safe for you to have/continue treatment	✓	✓	✓		✓		
11. Give a blood sample (optional to you) – to look at the level of cancer cells in your blood	✓		✓	✓	✓	✓	
12. Complete a Questionnaire about your quality of life. This should take about 30 minutes to complete and will be completed during a standard hospital visit	✓			✓	✓	✓ – this will be posted to you by your research team	✓– this will be posted to you by your research team

Your options

If I want to, will I definitely be able to take part?

Unfortunately, no. Although your doctor thinks you might be suitable to take part, they will still need to carry out some medical tests and ask you some questions to make sure the research is suitable for you. These are known as "eligibility screening tests" and are described below in the 'What happens if I decide to take part?' section. If the eligibility screening tests show that it is not suitable for you to take part in FOxTROT 4, your doctor will discuss alternative treatment options with you.

Do I have to take part?

No, your participation in FOxTROT 4 is entirely voluntary and you may stop at any time, without giving us a reason. If you decide to take part, you will be given this information document to keep. You will be asked to sign a consent form, but you are still free to stop at any time and without giving a reason.

If you decide not to take part or you initially agree to take part but later change your mind, your doctor will be happy to talk through alternative treatment options, for example the standard treatment of surgery followed by consideration of chemotherapy (to lessen the chance of your cancer coming back). Your treatment and care will not be affected in any way.

What happens if I decide to take part?

If you decide to take part, you will be given this information document to keep. Once your questions have been fully answered and you have gone through the consent form with your doctor, arrangements will be made for you to enter the research. You will be asked to sign a consent form, but you are still free to withdraw at any time and without giving a reason.

There are some further tests to be carried out in order to check if you are suitable to participate in the research. All the things that you will do as part of the research are shown in the Activity Summary Table on page 6 of this document.

<u>Screening</u>

- Blood tests
- An assessment of your medical history
- Clinical assessment
- Pregnancy test (only if you are female and pregnancy is a possibility)
- A CT scan of your chest/ abdomen/ pelvis
- An ECG (heart tracing)

- A stored tumour sample (biopsy) sent for MMR and BRAF^{V600E} testing (explained further below)
- Completion of quality-of-life questionnaires*

*Collecting information on your quality of life during and after treatment is really important and we appreciate the time it takes for you to complete the questionnaires. Completion is optional and this will not have any impact on your treatment. If you decide not to complete a questionnaire, you can change your mind next time and choose to complete the next questionnaire.

You would need to have some of these tests done even if you were not going to take part in this research, and some of them may already have been done as part of the investigations of your cancer.

During the Research

You will take some of the drugs daily as capsules (encorafenib) along with a drip every two weeks (cetuximab). You will be given a diary to record the number of capsules you take every day during this research and you should take this with you when you see your research team. This will help your research team keep records of any missed capsules.

There are laboratory tests that we will do on a tumour sample that has already been taken from you. The first is called a mismatch repair (MMR) test and the second is a test for the BRAF^{V600E} mutation as, if the cancer does not have this mutation, then the targeted therapy will not work.

For all participants taking part in FOxTROT 4, we need a small piece of your tumour when it is removed at your operation. This will also include photos of the biopsy and the part of your bowel containing the tumour removed at resection. This is sent to the FOxTROT laboratory at the University of Leeds. This is important so we can understand:

- How well the targeted therapy has worked.
- So that the FOxTROT research pathologists can 'carry out an in-depth examination of your tumour'. This makes sure that the same tests are done for all tumours regardless of what hospital you were treated in.

CT scans performed will be sent electronically to the FOxTROT research team at the Leeds Teaching Hospital Trust so that the FOxTROT doctors can make sure that all scans are treated the same in the research. The scans will be sent labelled with your name, date of birth, NHS/CHI number, the date of the CT scan and hospital name.

What are the possible side effects of the treatments?

All drugs given in this research are already in routine use for patients with your type of bowel cancer. Your doctors and nurses are therefore already quite familiar with them. You will receive targeted drugs called encorafenib and cetuximab.

Side effects of Encorafenib and Cetuximab

The table below shows all the common side effects that have previously been identified in people treated with encorafenib and cetuximab, with an indication of how likely these are to happen and guidance about whether they are potentially serious. Most side effects can be manged by using additional supportive medicines to help with symptoms.

Less Common side effects (may affect up to 1 in 1,000 or less than 1 in 100 people):
Less serious • Allergic reactions when treatments are given • Effects on the eyes including sore, dry or blurry eyes or less commonly inflammation of the eyes. • Effects on the heart including changes in heart tracings • Effects on the lungs
Common side effects (may affect up to 1 in 10 people):
Less serious • Feeling sick or being sick • Feeling tired (fatigue) • Skin changes such as an acne like rash or dry flaky skin • Hand foot syndrome where the skin of the hands and feet go red and skin can become dry, crack or blister. • Diarrhoea • Constipation • Tummy pain • Loss of appetite • Changes to your taste • Hair changes, hair can go more curly or brittle and some people may lose their hair (less common). Eyelashes may grow longer. • Muscle or joint pain • Difficulty sleeping • Headaches • Numb or tingling hands or feet (peripheral neuropathy) • Bleeding • Liver changes • Kidney changes • Skin cancer risk • Blood clot risk

Further information about encorafenib or cetuximab or (including how they are given and the side effects they may cause) can be found on the Macmillan charity's website at:

https://www.macmillan.org.uk/cancer-information-and-support/treatments-and-drugs/encorafenib-and-cetuximab

Visit the electronic Medicines Compendium (eMC) to download a Patient Information Leaflet (PIL) for more detailed information on each individual drug. The leaflet lists all known side effects.

https://www.medicines.org.uk/emc/

Your doctor or nurse can also provide you with a printed information sheet about these drugs.

How will my safety and progress be monitored?

a) You will be asked about any side effects that you may have experienced and will have a blood test at each treatment visit (for safety and research purposes). You may have an additional CT scan (on your chest/abdomen/pelvis) at the end of the neoadjuvant treatment. This will be around 2-4 weeks after finishing this treatment. Your doctor will tell you if this scan is necessary. You will have a second ECG (heart tracing) after one month of treatment. This would happen even if you were receiving encorafenib outside of this research.
b) You will also be asked to complete a questionnaire about your quality of life after completing neoadjuvant treatment.

You will of course be carefully monitored throughout your operation. Your surgeon will send the removed cancer for examination in the hospital's pathology laboratory and will discuss the results of the operation with you.

After you have recovered from the operation, you will be assessed by the oncologist and, when you are well enough, will discuss whether you would benefit from further chemotherapy. You will be monitored throughout this time for any side effects or other problems.

Regardless of whether or not you have chemotherapy after the operation, there will be a period of follow up, during which you will be asked to attend the clinic regularly for check-ups with occasional blood tests to assess your progress. These clinic visits will take place when you would usually be seen as part of your standard treatment, so you won't have to go to hospital more than usual. All participants will have a CT scan 3 years after starting the research to assess your progress. All participants will be asked to complete a questionnaire about your quality of life following your surgery and at 1 and 3 years after starting to participate in the research. After the 3-year CT scan and questionnaire, there will be no further research activities. However, you will move onto the standard NHS cancer surveillance programme of checks. The study team will request a yearly update of your condition from your hospital notes whilst the research is still open.

Pregnancy and contraception

If you are pregnant, think you may be pregnant, are planning on becoming pregnant, or planning to father a child you **must not** take part in this research. Also, you must not take part if you are breast feeding.

The drugs used in this research may be harmful to an unborn child. To prevent pregnancy, a highly effective method of contraception (with a failure rate of <1% per year) must be used by all women who can have children during treatment, and for six months after stopping your treatment. If in doubt, ask your doctor for clarification on the contraception method used.

Male participants who can father a child must use a highly effective method of contraception (with a failure rate of less than 1% per year) for the duration of the research and for 90 days after stopping treatment. If in doubt, ask your doctor for clarification on the contraception method used.

Please talk to your doctor if you have any questions. If you become pregnant during the treatment you must tell your doctor immediately and your research treatment will be stopped. If your partner becomes pregnant you should tell your doctor immediately. Your doctor will be able to advise you on the risks to your unborn child and discuss the pregnancy with you. It is important to tell your clinical care team if you are pregnant or become pregnant as this may affect your care. If you or your partner do become pregnant during your participation in the research, we will be obliged by law to request some basic information about the outcome of the pregnancy. This is so that organisations that monitor how medicines are used (such as the Medicines and Healthcare products Regulatory Agency [MHRA]) have the most up-to-date information about the effects of treatment.

Will my taking part be kept confidential?

If you decide to take part in FOxTROT 4, the information collected about you during the course of the research will be kept strictly confidential in the same way as all of your other medical records. Information about your disease and progress will be sent by your doctors to the FOxTROT 4 Research Office at the University of Leeds Clinical Trials Research Unit electronically or via post, where it will be handled confidentially and strictly in accordance with relevant data protection laws, including the Data Protection Act 2018. You will be allocated a research number, which will be used along with your date of birth and initials to identify you on each data form. Please refer to Part 2 and Part 3 of this Patient Information Leaflet if you require further information.

If you take part in the research, your relevant medical records may be inspected by authorised individuals from the research team, the University of Leeds (the research Sponsor); by the regulatory authorities; by authorised individuals from Pierre Fabre Ltd (the pharmaceutical company responsible for making encorafenib and who are providing funding for the research) to check that the research is being carried out correctly. Some of your data may be passed to Pierre Fabre Ltd to monitor the safety of encorafenib and to Merck (the pharmaceutical company responsible for making cetuximab) to monitor the safety of

cetuximab. This data will be fully anonymised so that you cannot be identified from the information.

Computed Tomography (CT) scans will be sent to Leeds Teaching Hospital Trust (LTHT) for central review, by our trial radiology team, to ensure that results are evaluated for all the hospitals involved in the trial in a consistent manner. These scans will be sent via standard hospital processes (such as electronic transfer, Royal Mail or courier). The scans will be labelled with your 'personal identifiable data': NHS/CHI identifier, hospital/site name, date of birth, date of scan and other site-specific identifiers for example patient name if required at your site. The purpose of collecting this data along with the scan, is so that we can be sure the CT scan being reviewed is for you and has the correct date. This data will be sent by a secure and encrypted method and once received at Leeds Teaching Hospital Trust, your 'personal identifiable data' will be removed and your CT scan will be saved with only your trial number.

The anonymised scans will be stored within the NHS and the University of Leeds, and authorised individuals may have access to this data to ensure the correct data has been provided.

In line with Good Clinical Practice guidelines, at the end of the research, your data will be securely archived for a minimum of 25 years by the University of Leeds (the research Sponsor). This is a requirement of clinical research and means that data can be checked at a later date if necessary. Arrangements for destruction of your confidential data will then be made.

Additional research

We would like to ask FOXTROT 4 participants for permission to carry out genetic testing on additional samples of your blood (these will be taken at the same time as your normal blood tests wherever possible, so just 'one needle prick') along with unused tissue from your tumour sample (taken in a biopsy) or unused tissue removed during your surgery. These samples may be used in additional research to learn more about bowel cancer and to see if it is possible to predict which patients will benefit most from each type of treatment and to test new ways of monitoring your condition after surgery.

We would like to ask FOXTROT 4 participants permission to use the stored CT scans and associated reports taken during the course of the research for future additional research to learn more about how earlier chemotherapy affects bowel cancer.

These samples and scans will be identified only by a code number, not your name, and neither you nor your relatives will be identified or contacted, and the results will not be added to your medical records.

We will also ask for your permission for any leftover samples, scans and data to be used in future research outside of the FOxTROT programme.

As these are additional studies, they will not affect your treatment in any way, and you are free to not consent to these and this will not affect your participation in FOxTROT 4 or your relationship with your doctor.

What will happen to any samples I give?

Blood and tissue samples you agree to have taken or collected for the research will be sent to laboratories outside of your hospital. These laboratories are carefully chosen by the Sponsor and legal agreements are in place specifically for this activity. These will be labelled with your research study number and a local laboratory number, they will not contain your name and address. These samples will be used to inform our understanding of which patients respond to therapy and the underlying reasons for different responses to treatment.

All samples will be sent to the laboratories using your hospital's standard processes or by a courier. When your samples are sent to the laboratories for further tests, there may be some of your samples left over once all the tests have been done. We will ask your permission to keep any of these left-over samples in storage so that they may be used for future cancer research. Any future research projects using your samples will need to be approved by an ethics committee. If you do not consent to your samples being stored and used for future research, blood samples will be destroyed at the end of this research. Your cancer tissue samples will be sent back to your local hospital for storage.

What will happen to the results of the research?

The findings from the research will be used to help improve care for people with bowel cancer. When the research is complete the results will be published in a medical journal, but no individual participants will be identified. We will make sure you have a chance to find out the results of the research if you would like them.

Part 2 – more about this research

What will happen if I don't want to carry on with the research?

You can stop taking part in all of this research, or in any part of it, at any time and without giving a reason. However, we would like to know the reason if you are willing to say, as this will help us understand if there are common reasons for participants to stop taking part in research. Before deciding to stop, you should talk to your research doctor or nurse. They can advise you and they may be able to deal with any concerns you may have. If you decide to stop taking part at any time it will not affect the standard of care you receive.

- If you decide to stop taking your research treatment (neoadjuvant treatment), you are likely to proceed to an operation after a period of recovery. Research follow up visits and assessments can still go ahead if you agree to this.
- If you tell us that you want to stop completing quality of life questionnaires, we will stop asking you to complete them. You can still take part in the research if you stop these, and you can change your mind later and start completing them again, if you want.
- If you decide to stop research follow up visits or assessments, to make sure the research is still reliable, we will need to keep the information we have already collected about you and include it in the research analysis.

Unless you clearly tell us you don't want us to, we will continue collecting information about your health from routine hospital visits, via your GP or through other contact between you and your hospital. This is to help ensure the results of the research are valid.

An important aim of the research is to find out how many participants complete their treatment and how people get on if they withdraw from treatment. For this reason, your data and samples would remain on file and be included in the final research analysis.

Finally, we will be legally required to collect information about any side-effects you have following your research treatment, even if you have told us you did not want to provide further data for the research.

Using your information for further research

When you agree to take part in research (and you have agreed to the using of your information for further research), the information about your health and care may be provided to researchers running other research programmes in this organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad.
Your information will only be used by organisations and researchers to conduct research in the public interest and in accordance with the UK Policy Framework for Health and Social Care Research (https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/uk-policy-framework-health-social-care-research/).

We will only share your information for worthwhile research with all appropriate approvals. We will only share your information in such a way that researchers outside the University of Leeds will not be able to identify you. The information will only be used for the purpose of health and care research and cannot be used to contact you or to affect your care. It will not be used to make decisions about future products and services available to you, such as insurance.

Involvement of your General Practitioner/Family Doctor (GP)

Your GP, and the other doctors involved in your healthcare, will be kept informed of your participation in this research.

Who has organised, reviewed and funded the research?

The FOxTROT research was developed by the National Cancer Research Institute's Colorectal Cancer Clinical Studies Group. The targeted treatments in FOxTROT 4 are being provided by two drug companies; Pierre Fabre Ltd will supply encorafenib and Merck will supply cetuximab. These companies are not involved in the day-to-day running of the research, and the responsibility for making decisions about the research design and how it is run will always remain with the doctors, statisticians, and research experts.

University of Leeds (the research Sponsor) has reviewed and approved this research and will be responsible for the management and conduct of the whole research. The day-to-day running of this research will be carried out by the Clinical Trials Research Unit (CTRU) at the University of Leeds.

The research has been reviewed and approved by all these organisations.
All research in the NHS is reviewed by an independent group of people called a Research Ethics Committee, to protect your safety, rights, wellbeing and dignity. This research has been reviewed and given a favourable opinion by a Research Ethics Committee. The project has also received approval by the Health Research Authority (HRA) and Medicines and Healthcare products Regulatory Agency (MHRA).

The Chief Investigator of all the FOxTROT research is Professor Jenny Seligmann (Consultant Medical Oncologist) who is based at St James's University Hospital, Leeds. The medical lead of FOxTROT 4 is Professor Janet Graham (Consultant Medical Oncologist) who is based at the Beatson West of Scotland Cancer Centre, Glasgow.

What will happen if I lose mental capacity during the research period?

There is no reason at all to suspect that you will lose your mental capacity as a result of taking part in this research. A head injury, for instance, could happen to anybody whether or

not they are taking part in this research, and should this happen to you, you could continue with your research treatment unless your doctor and your family or carer did not think this was in your best interests.

What if I have a concern or complaint?

Every care will be taken in the course of this research. However, in the unlikely event that you are injured as a result of design of the research or the managing organisation (University of Leeds), compensation may be available, however you may have to pay your related legal costs. Your hospital where you receive your treatment has a duty of care to you whether or not you agree to participate in the research and the University of Leeds accepts no liability for negligence on the part of your hospital's employees. If you wish to complain about any aspect of the way you have been treated, please contact your research doctor in the first instance.
Any claims will be subject to UK law and must be brought in the UK.

If you have private medical insurance, you should tell your insurer that you are taking part in research. They will let you know if it affects your policy.

If you wish to complain or have concerns about any aspect of the way you have been approached or treated during the course of this research, the normal National Health Service complaints mechanisms are available to you. Your healthcare team will give you further information if necessary. If you are unhappy about anything to do with this research and wish to complain formally, you can do this at the Patient Advice and Liaison Service (PALS). You can find your nearest PALS office on the NHS Choices website: http://www.nhs.uk/Service-Search/Patient-advice-and-liaison-services-(PALS)/LocationSearch/363. You can also ask your GP surgery, hospital, or phone NHS 111 for details of your nearest PALS.

Part 3 – Extra information about data protection

General information

The University of Leeds (the Sponsor for the research) for this research based in the United Kingdom. We will be using information from you and your medical records in order to undertake this research and will act as the data controller for this research. This means that we are responsible for looking after your information and using it properly. The University of Leeds will keep identifiable information about you for at least 25 years after the research has finished.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the research, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how we use your information at https://ctru.leeds.ac.uk/privacy/

As a university 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 research, we will use your data in the ways needed to conduct the research and analyse the findings.

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.
If you wish to raise a complaint on how we have handled your personal data, you can contact our Data Protection Officer 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).
Our Data Protection Officer can be contacted using the following details:

- Email: DPO@leeds.ac.uk
- General postal address: University of Leeds, Leeds LS2 9JT, UK
- Postal address for data protection issues: University of Leeds, Room 11.72 EC Stoner Building, Leeds, LS2 9JT
- Telephone number: +44 (0)113 243 1751

How will my information be used?

Your research doctor, nurse or other hospital staff will enter most of the information needed for the research directly into a secure research database held at the CTRU. You will be allocated a research number, which will be used along with your date of birth and initials to identify you on each form. Your full name will be included on your consent form and a copy

of this will be sent to the CTRU by fax or email so that we can check you have definitely agreed to take part in the research. If you completed a previous consent form to agree that some of your cancer sample could be sent to the central laboratory, this will also be sent to CTRU so that we can check this part of the consent.

Every effort will be made to ensure that any further information about you that leaves the hospital will have information removed so that you cannot be recognised from it; this information will usually be removed by a member of the research team at your hospital but may also be removed by the CTRU should they receive it.

Your healthcare records (including research data) may be looked at by authorised individuals from the research team, the University of Leeds (the research Sponsor) or the regulatory authorities to check that the research is being carried out correctly.

We would also like your permission to obtain information held within your electronic health records, including any hospital attendances and admissions and your health conditions from your GP and hospital records. We may use this for future research linked to this research, or for other research projects. We would only do this once any future projects had received ethical approval. To obtain your health record data, we would need to send a limited amount of your identifiable data (for example, initials, date of birth, and NHS number/CHI number) to the relevant data provider to obtain the correct information from these records. Other research teams may be involved in this future research, but they will not be able to identify you from the information provided to them.

We will do this because it is a more efficient way to collect certain data about your health. By using data collected from routine health visits, we can reduce the burden (such as the number of hospital visits) on you and your hospital. When we do this linking, we will only use the data mentioned above to identify you, and we will follow strict rules when working with other organisations to maintain confidentiality and to protect your data.

Unless you clearly tell us you don’t want us to, we will continue to obtain data about you if you stop taking research treatment or stop attending research visits. This is to help ensure the results of the research are valid.

CT scans and pathology blocks will be sent for central review to ensure that results / reports are consistent across hospitals. Pathology blocks will be sent via standard hospital processes (such as Royal Mail or courier). CT scans will be sent electronically via secure electronic transfer. Wherever possible, this data will be anonymised and your name removed.

Your NHS hospital will use your name, NHS number/ CHI number and contact details to contact you about the research, and make sure that relevant information about the research is recorded for your care, and to oversee the quality of the research. Individuals from the University of Leeds and regulatory organisations may look at your medical and research records to check the accuracy of the research. Your NHS hospital will pass these details to the University of Leeds along with the information collected from you and your medical records. The only people in the University of Leeds who will have access to information that identifies you will be people who audit the data collection process. The people who analyse

the information will not be able to identify you and will not be able to find out your name, NHS number/ CHI number or contact details.

The University of Leeds (the research Sponsor) will collect information about you for this research from your medical team. This information will include your name, date of birth, postcode, and health information, which is regarded as a special category of information. We will use this information to monitor your progress. Your postcode is being collected as it can help us understand the diversity of our participants and to know if the participants in this research are reflective of the overall population.

Your NHS hospital will keep identifiable information about you from this research for at least 25 years after the research has finished.

What if there is a problem?

If a medical emergency related to your treatment in this research occurs while you are at home, you should contact the hospital where you received your treatment or you should go to the Accident and Emergency (A&E) department of your local hospital. You can also dial 999 as with any medical emergency. If the problem is not an emergency and you are unable to get to the hospital you should contact your GP.

Meet the team

Our highly experienced and friendly research team at *(insert site name)* will look after you as part of this research. Here are some of the team members that you may see during your visits.

Insert site specific photos of clinicians that the participants are likely to see/interact with and their names/roles. If individual sites are not comfortable in providing this, then please delete this part of the PIS.

If you have any questions, please talk to <<Enter PI, nurse name >> at << Contact details for site>>

Contact information

Contact details:

Urgent contact details

Non-urgent contact details

Delete this line, then print on Trust/Hospital headed paper

Patient ID:	Initials:
Date of Birth:	NHS/CHI Hospital Number:
EudraCT Number: 2021-002216-31	Principal Investigator:

PATIENT CONSENT FORM FOR ENROLMENT INTO THE MAIN RESEARCH (FOxTROT 4)

Please initial each box

1. I confirm that I have read and understand the information document for the above research and have had the opportunity to ask questions. ☐

2. I understand that my participation in this research is voluntary and that I am free to withdraw at any time without my medical care or legal rights being affected. I understand that even if I withdraw from the above research, the data and samples collected from me will be used in analysing the results of the research and in some cases further information about any unwanted effects of my treatment may need to be collected by the research team. ☐

3. I understand that my healthcare records may be looked at by authorised individuals from the research team, regulatory bodies or Sponsor in order to check that the research is being carried out correctly. ☐

4. I agree for my necessary details (including my name, date of birth, NHS/CHI number, the date of the CT scan and hospital name) to be sent to Leeds Teaching Hospital Trust to allow for study review of my CT scan . ☐

5. I understand that some of my data may be passed to other organisations, such as the pharmaceutical companies Pierre Fabre and Merck, (possibly in other countries where the data protection standards and laws may be different from the UK) to monitor the safety of the treatment(s) that I am receiving. I understand that my identity will remain anonymous ☐

6. I agree to a copy of this Consent Form being sent to the Leeds Clinical Trials Research Unit, along with a copy of my previous consent form (for sending cancer tissue to central laboratory) if applicable. ☐

7. I agree that my GP, or any other doctor treating me, will be notified of my participation in this research. ☐

8. I agree to take part in the research. ☐

The following points are OPTIONAL

Even if you agree to take part in this research, you do not have to agree to this.

I give permission for surplus samples from my cancer sent to the FOxTROT research laboratories at the Universities of Leeds and Birmingham to be stored and used for future cancer research that is subject to ethical approval. I understand that my name will not be included on the samples, but they will be labelled with a unique reference number that will allow the sample to be linked back to data collected through the main research in future, for research purposes. I understand that my tissue samples are a 'gift' from me to the sponsor and I expressly request that they are shared for the purposes of future cancer research. I understand my tissue samples may be shared on a collaborative basis with researchers in the UK and possibly abroad, including outside the European Economic Area. This may include commercial organisations. I understand that my tissue samples may be used for genetic research. I understand that data collected about me will also be shared so that the results of the research can be interpreted properly.

Please tick ✓

Yes ☐ No ☐

I give permission for an extra blood sample to be taken to look at the level of cancer cells in my blood. I agree to these samples being stored and used for additional research investigations that form part of this research. I understand that strict confidentiality will be maintained at all times and that my name and individual details will not be stored with my samples (i.e. they will be anonymised). However, a unique reference number will be allocated to the samples which may allow them to be linked back to me in future for research purposes.

Yes ☐ No ☐

I give permission for my CT scans and the associated CT reports to be stored and used for future cancer research that is subject to ethical approval. I understand that my name will not be included on the scan/report, but they will be labelled with a unique reference number that will allow the scan/report to be linked back to data collected through the main research in future, for research purposes.

Yes ☐ No ☐

I agree to allow any information or results arising from this research to be used for healthcare and/or further medical research. I understand that if the information or results from this research are shared my name, contact details and any other details which identify me (such as NHS number/ CHI number, date of birth, postcode) will not be shared.

Yes ☐ No ☐

I give permission for my postcode to be collected.

Yes ☐ No ☐

Patient:

Signature……

Name (BLOCK CAPITALS)……

Date……

Investigator:
I have explained the research to the above-named patient and he/she has indicated his/her willingness to participate.

Signature……

Name (BLOCK CAPITALS)……

Date……

(If used)Translator:
Signature……

Name (BLOCK CAPITALS)……

Date……

Independent Witness:
I have completed this consent form on behalf of the person named above who has freely given their consent to participate.

Signature……

Name (block capitals)……

Date……

I. (1 copy for patient; 1 for the CTRU; 1 held in patient notes, original stored in Investigator Site File)

Note for Investigators regarding remote consent: If the study has been explained to the patient remotely (over telephone/video call), the patient should sign and date on the day of the conversation. The Investigator (or research nurse if at registration) should then review, sign and date the form once this has been posted back to the research team.
Please tick here if consent was provided remotely: ☐

Patient Question Sheet (For your use)

No.	My Question/Notes	On Page No.	Answer Received
1.			
2.			
3.			
4.			
5			
6.			