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EMT2: EPA for Metastasis Trial 2

PARTICIPANT INFORMATION SHEET AND INFORMED CONSENT DOCUMENT

A large-print version of this sheet is available on request.

You have been invited to take part in a research study called EMT2, funded by Yorkshire Cancer Research. Before you decide if you want to take part, we would like to explain why the research is being done, how we will use the information we have about you, and what the study will involve.

Please read this information carefully, and discuss it with others if you like. Ask us if anything is unclear, or if you would like more information.

Once you have read this information, your doctor or research nurse will talk to you about the study again and you can ask any questions you like.

- Part 1 tells you the purpose of this study and what will happen to you if you take part.
- Part 2 gives you more detailed information about the conduct of the study.

Take time to decide whether or not you wish to take part.

How to contact us

If you have any questions about this study, please talk to your doctor at

<<Enter PI, nurse name >>

<< Contact details for site>>

Thank you for reading this information sheet.

Part 1

What is the purpose of the study?

EPA is an omega-3 fatty acid which is a natural substance found in fish like salmon and mackerel. In a previous small trial (the first EMT trial) we found that people who had received bowel (also known as colorectal) cancer treatment, but had gone on to develop liver spread (metastasis), experienced a possible benefit from taking EPA capsules before their surgery to remove the liver metastasis. However, the previous study only involved a small number of people and it was not able to show for sure whether EPA had a beneficial effect.

The purpose of the EMT2 study is to find out if there definitely is a benefit in taking EPA capsules before liver surgery, which will be possible by involving a larger number of people in the study. Unlike the first EMT study, EMT2 is also looking at whether there is also benefit from taking EPA capsules after surgery (for up to 4 years).

Why have I been chosen?

You have been invited because you are in the group of patients that we think may benefit from the proposed treatment. You have colorectal cancer liver metastasis that is due to be removed by surgery.

Do I have to take part?

No, your participation in EMT2 is entirely voluntary. If you decide not to take part, your treatment and care will not be affected in any way. If you join the trial, you may withdraw your consent to take part 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 withdraw at any time and without giving a reason.

What is the standard treatment?

The standard treatment is to have your liver metastasis removed by surgery. If your doctor considers it is appropriate in your case, you may also receive chemotherapy following your surgery.

EPA has no equivalent in current standard treatment before or after liver surgery.

What will happen to me if I take part?

The best way of finding out whether EPA is effective is in a randomised study. 'Randomised' means that a computer will allocate you randomly (as if by the roll of dice) to receive either EPA capsules or dummy (placebo) capsules. Neither you nor your doctor will choose or know which treatment you receive. In this way, a fair and unbiased comparison can be made.

As EPA has no equivalent in current standard treatment, it is important that a placebo is used in the study. Without a comparison with the placebo, we will not know whether EPA has any benefit compared with no treatment at all.

Although it is unlikely to happen, if you become unable to make medical decisions after you have entered the trial, your clinician will consult your family and any decisions will be made in your best interest. Your decision to participate in the trial will be respected.

What is EPA?

EPA stands for eicosapentaenoic acid which is one of the main omega-3 fatty acids that are found naturally in fish. Fish oil capsules available on the high-street contain a mixture of different omega-3 fatty acids (usually about 30% EPA) but the EPA capsules tested in this trial (called Vazkepa® in the UK and Europe; Vascepa® in the USA) are much purer (100% EPA) and provide a significantly higher dose of EPA (4 grams per day) than commercially available omega-3 supplements. The EPA capsules used in the trial are licensed for prevention of cardiovascular problems including heart attack and stroke in individuals with certain risk factors.

The capsule shell contains gelatin of animal origin so is not suitable for vegetarians. The shell also contains a small amount of sorbitol, maltitol and soya lecithin, which should be avoided by individuals with rare hereditary problems with fructose intolerance or allergy to soya or peanut.

What is a placebo?

The placebo capsules are a 'dummy' that look identical to the EPA capsules, but do not contain any EPA. The placebo capsules contain the same amount of inert light mineral oil. They should be taken in the same way as the EPA capsules.

The capsule shell is made using the same ingredients as the EPA capsules and contains gelatin, sorbitol, maltitol and soya lecithin.

Will I be told if I am having EPA or placebo?

No, this is a double-blind study which means that neither you, nor your doctor will know if you are receiving EPA or placebo. The capsules and the packaging used are specially designed to make sure that you cannot tell them apart. However, if you have any problems whilst receiving your treatment, your doctor will be able to find out which treatment you are receiving. If, at the end of the trial (once the trial results are available), you would like to know which treatment you received, you should speak to your doctor who will be able to obtain that information for you.

How long does treatment go on?

Whichever capsules you receive, you will start treatment before the day of your liver surgery and continue for at least 2 years and up to 4 years, after your surgery. The trial will be open for at least 2 years after the last participant enters the trial so how long you continue on trial treatment depends on when you join the trial.

When and how do I receive treatment?

Whichever capsules you receive, you will take 4 capsules per day with food. It is suggested that you take 2 capsules in the morning with your meal and 2 capsules in the evening with your meal but you can alter this schedule to suit yourself.

You will be given a new box containing 7 new bottles at trial visits or after a trial telephone call (unless you already have enough capsules to last until your next visit). This can be collected from the hospital Pharmacy or delivered via courier if you live far away from the hospital and further hospital visits are not possible. Please remember to check the expiry date which is recorded on the box and the bottles to ensure that the medication you are taking is in date. You will also be given a Drug Tracking Card which you can use to record the expiry dates of all the capsules you have been dispensed. Please bring the box and all the unused bottles with you at each clinic visit so that your doctor or nurse can check whether you need more capsules. For those receiving capsules via courier, any unused capsules will be collected at the end of the trial by post and you will receive full instructions in due course.

It is very important that you do not take extra omega-3 fatty acid supplements during the trial. These include fish oil or cod liver oil supplements. These may affect the results of the trial and could mean that you inadvertently take extra EPA over the recommended dose. If you are unsure about a particular supplement you wish to take, please speak to your research nurse or doctor.

If your medication has expired, please return the box and all unused bottles at your next clinic visit.

Unwanted effects of treatment

Omega-3 supplements are widely available and have been used safely for many years. Omega-3 fatty acids have an excellent safety record.

The large clinical trial (more than 8000 patients) of the same dose of EPA capsules used in the EMT2 trial concluded that the treatment was safe. There was a small increased risk of irregular heart rhythm (atrial fibrillation), which was greater in patients with previous atrial fibrillation. In the trial, atrial fibrillation occurred in 5.8% of patients receiving EPA capsules compared with 4.5% of individuals who received the placebo. In the same trial, there was also a small increased risk of all types of bleeding in patients receiving EPA capsules (11.8%) compared with individuals who received placebo (9.9%).

Overall, the most frequently reported side effects of other forms of EPA and omega-3 fatty acids, in general, are all mild with gastro-intestinal problems like diarrhoea, abdominal cramps, nausea, bloating, halitosis (bad breath), belching, indigestion and a fishy aftertaste being possible in no more than one fifth of users. These side effects can be minimised by taking the capsules with food. Everyone's reaction to the capsules will be different and it is difficult to predict if you will experience any side effects at all. The important thing is to tell your doctor or nurse if you are having any problems with the capsules. If a side effect occurs and persists, your doctor or nurse will advise you on what action to take.

Pregnancy during treatment, information for women and/or men

If you are a woman, it is important to tell your clinical care team if you are pregnant or become pregnant as this may affect your care. If you are a man, it is important to tell your clinical care team if your partner becomes pregnant.

It is believed that EPA is entirely safe in pregnancy and eating oily fish containing EPA is of course permitted during pregnancy. However, we don't yet know for sure whether the EPA capsules should be taken during pregnancy or by couples trying for a baby. Therefore both women and men must make sure to use a reliable form of contraception while taking the trial capsules.

When will the study visits be and what will happen during them?

If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form.

It is expected that the trial visits/telephone calls will closely mirror the follow-up visits you would receive as part of standard care so you may not need to have any additional visits. However, depending on when you last attended clinic at the time the trial closes, you may need to have a trial-specific appointment at the end of the trial.

Depending on when you join the study, you will need to attend your local hospital or take a telephone call about the trial between 10 (if you are in the trial for the maximum of 4 years) and 5 times (if you are in the trial for the minimum of 2 years). You will need to attend the following visits:

- A visit before the day of your liver surgery (which may be the visit today if you are happy to join the trial today. If you would prefer to have more time to think about it, you can come back for a visit before your liver surgery)
- A visit from the research nurse during admission for liver surgery
- Follow up visits/telephone calls at 6 monthly intervals after your liver surgery

The visits that you can expect to have are shown in the table below. These will be

linked to the standard scheduled hospital visits wherever possible.

The CT scans that you have will be the routine scans that would be performed as part of your routine care. . You will have a CT scan prior to visits 3, 4, 5, 6, 8 and 10. However, you may need to have an extra CT scan during visit 10 if it has been less than 6 months since your last clinic visit/telephone call at the time that the trial closes.

Your research nurse or doctor will also contact you by telephone fortnightly between your first visit and your liver surgery and once 60 days after you finish treatment to ask how you have been feeling since they last spoke to you, about any other medications that you are taking and if you have attended hospital or your GP for any reason.

At the majority of your hospital visits/telephone calls you will be asked to complete three questionnaires about your quality of life and one questionnaire about the number of times you have visited a health professional (eg your GP/practice nurse). You will also be asked to complete one questionnaire at your final trial visit to let us know whether you think you have been receiving EPA or placebo capsules. These questionnaires may take around 10 to 30 minutes of your time, depending on the number of questionnaires required at the visit.

Visit type and timing*	**Duration of visit**	**Visit details**
Visit 1 (start of trial)	2 to 2½ hours	• Sign consent form • Medical history • Complete 4 questionnaires • Blood test • Collect prescription
Fortnightly phone call	Phone call only	
Visit 2 (in hospital for liver surgery)	½ hour	• Complete 1 questionnaire • Blood test • Collect prescription
Visit 3 (6 months after surgery)	2 hours	• Review of CT scan • Complete 4 questionnaires • Blood test • Collect prescription
Visits 4 - 9 (6 monthly)	2 hours	• Review of CT scan (at visits 4, 5, 6 and 8) • Complete 4 questionnaires Collect prescription
Visit 10 (6 months after visit 9) **or Exit visit** (<6 months after last visit)	2 hours	• Review of CT scan • Complete 5 questionnaires

Phone call (60 days after last visit)	Phone call only	

*'visit' may be to a hospital clinic or a trial-specific telephone call if the hospital is distant from your home or a visit is not possible. You will be given a Participant Diary booklet that you can use to record information that you will need to know at your clinic visit. This includes the number of times you saw your GP, practice nurse or other healthcare practitioner, the number of times you took less than the prescribed number of capsules and when you felt unwell.

You will have a blood sample taken at your first three trial visits. This is to measure the amount of EPA that has been incorporated into your blood cells. This will give us a good idea about whether EPA is working. Neither you nor your doctor will be informed of the results of these tests.

Please note that, unfortunately, we are unable to cover the cost of any extra journeys or parking costs that may be involved as a result of participating in this study.

What are the possible disadvantages and risks of taking part?

Being involved in this research study involves time and commitments such as regular hospital visits, telephone calls, some additional tests and the time spent completing the questionnaires.

You will be asked to have three blood tests. These are the same as normal blood tests that you will have had before. As with any blood test, there is a small risk of bruising and discomfort, and very rarely infections.

Ionising radiation

Most of the CT scans are part of your routine care. If you take part in this study you may undergo one additional scan. These procedures use ionising radiation to form images of your body and provide your doctor with other clinical information. Ionising radiation can cause cell damage that may, after many years or decades, turn cancerous. The chance of this happening to you as a consequence of taking part in this study is extremely small.

What are the possible benefits of taking part?

If you agree to take part in EMT2, there may or may not be a direct medical benefit to you. Whether you receive EPA or placebo, you will be making an important contribution to this clinical trial and cancer research in general. Clinical trials are essential for progress in the development of new treatments. Although we cannot guarantee that the treatment will be beneficial to you, the results obtained from this study will provide important information which may help other people in the future who are

diagnosed with colorectal cancer and liver metastases.

What if something goes wrong?

We do not expect anything to go wrong. Omega-3 supplements have been used safely for many years and the EPA capsules that are being used in the trial are licensed for use for prevention of cardiovascular problems like heart attack. The trial team and an independent review committee will closely monitor the trial on an on-going basis so that if there are any problems they will be detected as soon as possible so that the trial can be changed or stopped if necessary. If you experience problems, you must report these to your research nurse or doctor.

What happens when the research study stops?

The trial will close two years after the last person joins the trial and all participants will stop trial treatment at this time. You will stop taking trial treatment capsules on the day of your last clinic visit/telephone call.

At the end of the study, you can discuss with your usual doctor if you feel you have benefited from your treatment on the study. However, we cannot guarantee that your doctor will be able to prescribe EPA for you in the form the trial used at the end of the study as it is not currently available as a treatment on the NHS.

Additional research

We will be looking at the changes in your muscle size to see if EPA helps to reduce the muscle and weight loss that can be caused by cancer. To do this, we will collect your CT scans and compare the size of muscle around your spine over the course of the trial, including the scan that you have before you enter the trial to confirm your liver metastasis.

Any remaining blood samples may be transferred to the Leeds NIHR Biomarker Biobank and stored for use in a range of research projects in order to find new ways to diagnose, treat and prevent liver disease. The samples that you provide will be treated as gifts that could help research to benefit those affected by liver disease in the future. All such work is anonymous; your sample will be identified by a code number, not your name, and you will not be identified or contacted.

Will my taking part be kept confidential?

If you decide to participate in EMT2, the information collected about you will be handled strictly in accordance with the consent that you have given and also the Data Protection Act 2018. Please refer to Part 2 for further details.

Contact Details

If you have any further questions about your illness or clinical studies, please discuss them with your doctor or research nurse. You may also find it helpful to contact Macmillan Cancer Support, an independent cancer information charity (freephone: **0808 808 00**

00; address: 89 Albert Embankment, London, SE1 7UQ; website www.macmillan.org.uk) or CancerHelp, an information service about cancer and cancer care for people with cancer and their families by Cancer Research UK (Tel: 020 7061 8355; website www.cancerhelp.org.uk). If you would like further information about clinical research, the UK Clinical Research Collaboration (a partnership of organisations working together on clinical research in the UK) have published a booklet entitled 'Understanding Clinical Trials'. Contact UKCRC: Tel: 0207 670 5452; website www.ukcrc.org

This completes Part 1 of the Information Sheet. If the Information in Part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision.

Part 2

What if relevant new information becomes available?

Sometimes during the course of a study, new information becomes available. If this happens, your doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide not to continue your doctor will continue your care if this is necessary. If you decide to continue you may be asked to sign an updated consent form. Occasionally on receiving new information, your doctor may consider it to be in your best interest to withdraw you from further study treatment.

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

If you withdraw consent for further study treatment, information will still be collected about you, unless you request otherwise, and it will be included in the final study analysis. If you withdraw consent for further data collection your data will remain on file and will be included in the final study analysis. The EMT2 Study Team may be required to collect some limited information about you about side effects you may have as a result of taking part in the trial. This will only be collected if required by the Regulatory Authorities. In line with Good Clinical Practice guidelines, at the end of the study, your data will be securely archived for a minimum of 15 years. Arrangements for confidential destruction will then be made.

Who has organised, reviewed and funded the research and who will be supervising it?

The Chief Investigator is Professor Mark Hull who is based at the University of Leeds. He is a Consultant Gastroenterologist and an expert in the molecular basis of colorectal cancer development and colorectal cancer prevention. The study is being sponsored by the University of Leeds and is organised on its behalf by the Clinical Trials Research Unit (CTRU) at the University of Leeds. The study will be taking place in at least 8 different hospitals in the UK. The study has been reviewed and funded by Yorkshire Cancer Research (YCR). It has also been reviewed by North East: Newcastle and Tyneside 2 Research Ethics Committee.

What if there is a problem?

In the very unlikely event of a medical emergency, related to your treatment for this study, occurring while you are at home, you should initially try to contact the unit where you received your treatment (contact details are on the first page of this document). If this is not possible you should go to the Accident and Emergency (A&E) department at your local hospital. If you are unable to get to the hospital you should contact your GP who, with your consent, will already have been informed of your participation in the study.

Complaints:

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 study, the normal National Health Service complaints mechanisms should be available to you. Your doctor will give you further information if necessary.

Harm:

Every care will be taken in the course of this clinical trial. However, in the unlikely event that you are injured as a result of the trial, the managing organisation (University of Leeds), may pay compensation but 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 trial 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.

Will my taking part in this study be kept confidential?

If you decide to participate in EMT2, the information collected about you will be handled in accordance with the consent that you have given and also the Data Protection Act 2018. The information needed for study purposes will be collected on paper forms

and sent (usually using standard Royal Mail post but in some cases by fax or email) from the hospital to the CTRU.

You will be allocated a study number, which will be used along with your date of birth and initials to identify you on each paper form. Your full name will be included on your consent form and a copy of this will be sent to the CTRU by fax, post or email. Every effort will be made to ensure that any further information about you that leaves the hospital will have your name and address removed so that you cannot be recognised from it; this information will usually be removed by a member of the study team at your hospital, but may also be removed by the CTRU upon receipt.

If you have your study medication delivered by post, your name and address will be on the invoice sent by the courier to CTRU. This information will be used for invoicing purposes only.

Your data will be entered onto a secure database held at the CTRU in accordance with the Data Protection Act 2018.

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

Your name, date of birth, and NHS number may be submitted to standard NHS registries such as Hospital Episodes Statistics (a standard NHS patient registry held by the Health and Social Care Information Centre and other central UK NHS bodies). This is so that information about your health status and hospital attendance may be obtained by the CTRU.

The information collected about you may be shared with other research teams to answer new research questions in the future. This may include information from the NHS registries on how you are doing after you finished participating in the trial. Wherever possible, information will be anonymised (for example; your full name will not be disclosed).

Your data may be shared with the research team at the Institute of Cancer Therapeutics at the University of Bradford, who will be responsible for analysing the trial blood samples.

CT scans and blood samples will be sent for central review to ensure that results / reports are consistent across hospitals. These will be sent via standard hospital processes (such as Royal Mail or courier). This data will be anonymised and your name removed.

Your data may be passed to other organisations (possibly in other countries where the data protection standards and laws are different to the UK) to monitor the safety of the treatment(s) that you are receiving; this data will have your name removed.

Involvement of the General Practitioner/Family Doctor (GP):

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

What will happen to any blood samples, I give?

Your blood samples will be stored at your local hospital until they are collected by courier and transferred to the Institute of Cancer Therapeutics at the University of Bradford where they will be tested to measure the amount of EPA in your red blood cells.

Any remaining samples and data may also be stored in the Institute of Cancer Therapeutics at the University of Bradford and may provide a resource for future studies in colorectal cancer. If any information from this study is used to develop new research, data protection regulations will be observed and strict confidentiality maintained; your data will have your personal details removed, but will be coded so it can be linked back to your details. You will not be identified in the results of future studies. Ethical approval will be obtained for any future studies involving your data or samples.

You can change your mind about participating in the Institute of Cancer Therapeutics research at any time by contacting your trial clinical team. You do not need to tell us why.

You will not receive any personal financial reward for gifting your samples to future research.

Will any genetic tests be done?

No.

What will happen to the results of the research study?

When the study is complete the results will be published in a medical journal, but no individual participants will be identified. If you would like to obtain a copy of the published scientific results, please ask your doctor. The trial team also aim to write a summary of the trial results for the public and publicise the results in the media. If at the end of the trial, once the results of the study are available, you would like to know which treatment you received you should speak to your doctor who will be able to obtain that information for you. You will not be told which treatment you received before then unless your doctor feels that there is a medical reason to do so.

Thank you very much for reading this information sheet.

If you have any questions, please ask us.

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

Participant ID:	Initials:
Date of Birth:	NHS/Hospital Number:
EudraCT Number:	Principal Investigator:

EMT2: EPA for Metastasis Trial 2

PARTICIPANT CONSENT FORM

Please initial each box

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

2. I understand that my participation in this study 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 study, the data and samples collected from me will be used in analysing the results of the study and in some cases further information about any unwanted effects of my treatment may need to be collected by the study team. ☐

3. I give permission for blood samples to be taken, stored and tested by the Institute of Cancer Therapeutics at the University of Bradford. 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. I agree to these samples being stored and used for additional ethically approved research investigations in future research. ☐

4. I understand that my healthcare records may be looked at by authorised individuals from the study team, regulatory bodies or Sponsor (University of Leeds) in order to check that the study is being carried out correctly. ☐

5. I agree to allow any information or results arising from this study to be used for healthcare and/or further medical research upon the understanding that my identity will remain anonymous wherever possible. ☐

6. I understand that the information held and maintained by NHS Digital and other central UK registries may be used to help contact me or provide information about my health status during the trial and in the future. I agree for my details (which will include my name, date of birth and NHS number) to be submitted to these bodies so that information about my health status may be obtained by the CTRU if necessary. ☐

7. I agree to a copy of this Consent Form being sent to the CTRU. ☐

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

9. I agree to take part in the study. ☐

Patient:

Signature……

Name (block capitals)……

Date……

Investigator:

I have explained the study 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……

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