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Patient Information Sheet

MISSION-Fumarate: A physiological study of the metabolism of fumarate in cancer using hyperpolarised ^{13}C magnetic resonance imaging

We would like to invite you to take part in a clinical research study. Before you decide whether or not to take part, it is important for you to know why the research is being undertaken and what it will involve for you. Please take time to read the following information carefully before making your decision and discuss it with others if you wish. Please ask us if there is anything that is unclear or if you would like more information using the contact details at the end of this document.

If you are satisfied with the information provided and would like to take part in this study, you will be asked to sign a consent form; a member of the research team will also sign it. You are free to change your mind about taking part even after you have signed the consent form.

This information sheet is divided into two parts:

- Part 1 tells you why the study is being carried out and what will happen if you take part
- Part 2 gives more detailed information about how the study is carried out

Part 1

What is the purpose of this study?
The first purpose of this study is to better understand in detail what is happening to patients with cancer by using a new imaging technique named 'Hyperpolarised Magnetic Resonance Imaging (MRI)'. By analysing images collected from both patients and healthy volunteers and then comparing those to tissue samples (e.g. biopsies) collected from patient's tumour we want to increase our knowledge of what is happening inside a tumour. The second purpose is to see if this new technique can be used to predict who will have a better, more effective, response to treatment and if this can be achieved at an earlier point during treatment. We hope that results of this study will help us to design new and better ways to image patients with cancer.

What is Hyperpolarised MRI?
Hyperpolarised Carbon (^{13}C) MRI is very similar to a standard MRI, except that you will receive an injection of hyperpolarised fumarate (fumarate is a molecule which is found naturally in your body and is linked to cell death) through a small plastic tube (called a cannula). Hyperpolarised Fumarate is not radioactive. The reason we hyperpolarise the fumarate molecule is to greatly increase the signal above natural levels so the MRI scanner is able to identify this in your body. This helps us to determine how tumour tissue processes and converts fumarate and can compare this to other participants.

Why have I been invited?
We are inviting up to 70 patients diagnosed with cancerous tumours or masses and you have been identified by your clinical care team as a potential participant who meets the criteria for the research.

Do I have to take part?
No, taking part in this study is entirely voluntary. If you decide to participate, you are free to withdraw from the study at any time, without giving a reason. Withdrawal or refusal to participate will not in any way affect the standard or type of care you will receive from the clinical team who are looking after you.

Who is organising and funding the study?
The study is being conducted by the Department of Radiology, University of Cambridge and Cambridge University Hospitals NHS Foundation Trust. The study is being funded by Cancer Research UK (CRUK), The Mark Foundation and the National Cancer Imaging and Translational Accelerator (NCITA).

What will happen if I take part*?*
If you decide to take part, additional procedures will be performed beyond those normally required by your clinical team and these are shown in the study flowchart below. Some of these events can occur during the same visit and wherever possible we will attempt to undertake these on the same day to avoid multiple visits. Study assessments may include, but not limited to, checks of blood pressure, heart rate, oxygen saturation, blood samples (up to 50 mL) and pregnancy test (where applicable).

It is unlikely that you will gain any immediate benefit from these additional procedures, but the discoveries we make may help future patients with similar conditions to you.

At the MRI scanning visits (shown overleaf), you will have a standard MRI scan and hyperpolarised MRI scan where you will receive an injection of hyperpolarised fumarate while laying inside the MRI scanner. Depending on the type of tumour or mass you have, will determine your position and how you lie on the MRI bed. This will be discussed with you by a member of the research team prior to the day of scanning. The two scans are performed to compare and contrast the information we gather from the Hyperpolarised MRI. In total the examination (including pre and post study assessments) will last up to two hours. No patient will be asked to undertake more than four Hyperpolarised MRI injections. You will be asked if you wish to have an **optional** scan and injection within five days of the first injection for testing of repeatability.

Criteria that may exclude you from participating
If any of the below apply to you, please let a member of the research team know and we will discuss options with you (contact details at the end of this document).

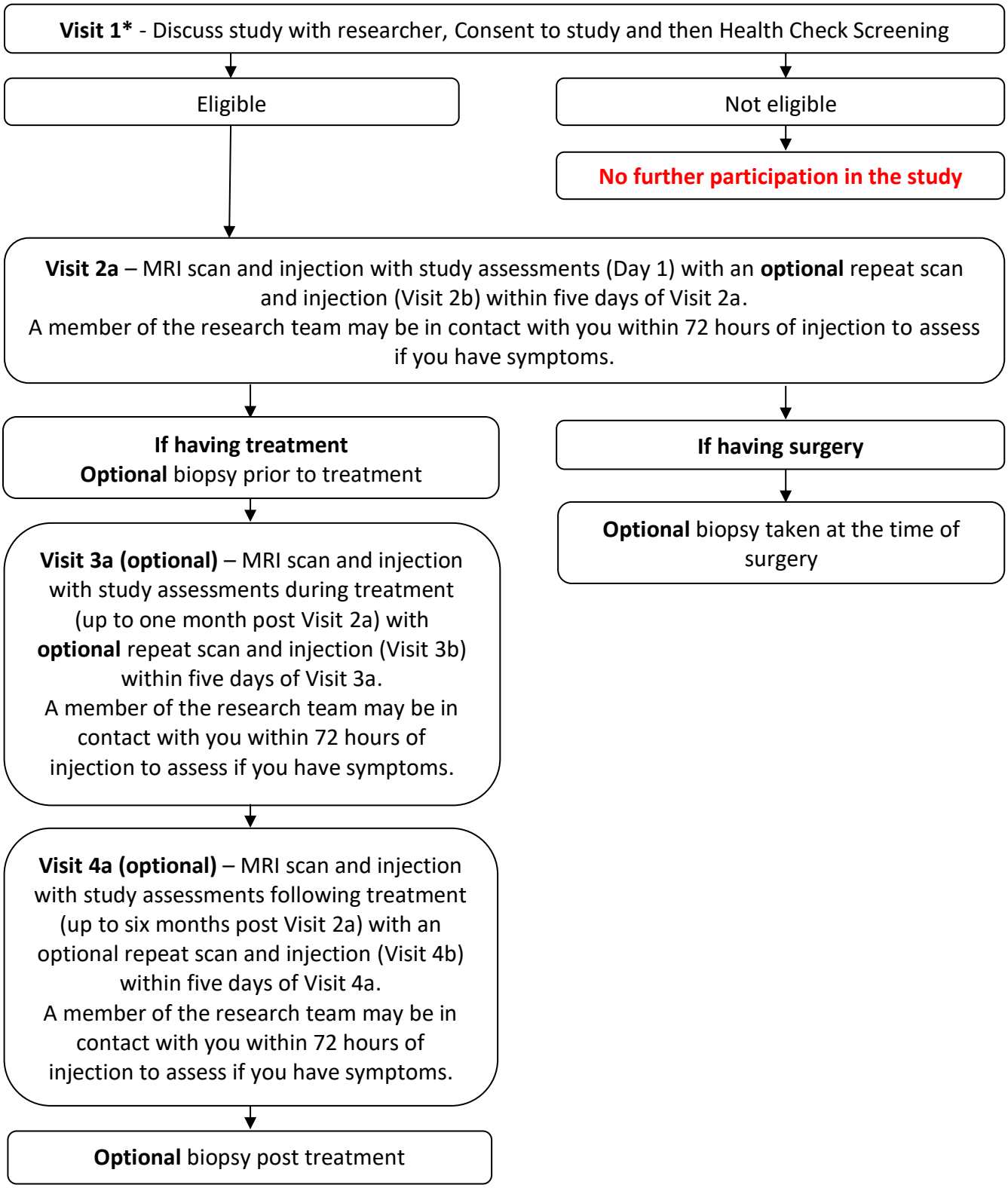
You may not be eligible to take part in the study if you:

- Have a heart pacemaker, a cardiac stent, an inner ear (cochlear) implant, or certain metallic devices such as a copper-coated intrauterine contraceptive device (coil).
- Have a known allergy to the MRI contrast agent (called Gadolinium)
- Have poor kidney function that would not allow you to have MRI contrast injected (this will be checked prior to the first scan and injection)
- Are pregnant, breast feeding or trying to get pregnant

Women of childbearing potential are required to use adequate contraception for at least two weeks prior to hyperpolarised injection and up to two weeks following hyperpolarised injection and a pregnancy test will be performed prior to each injection. Men are also required to use adequate contraception (e.g. barrier methods such as condoms) for up to two weeks following a hyperpolarised injection as a precaution. Details of what is classed as adequate contraception will be discussed with the researcher prior to consent.

Study Flow chart for patients

Patients will not undergo more than four hyperpolarised injection



* For Visit 1, we will aim to undertake health check screening on the same day as your other appointments. This is to limit the number of times you need to visit the hospital

What are the possible benefits of taking part?
We hope that this study will help develop new ways of imaging tumours and seeing how they respond to treatment, without patients having to have invasive procedures such as biopsies. This could also help to predict which patients will respond to which treatments with more accuracy. There are unlikely to be direct benefits to you from taking part. However, all images from the standard MRI acquired will be reviewed by a radiologist and any unanticipated findings will be reported to your clinical team to discuss if further investigations are needed.

Reimbursements
You will not receive any payment for participating in this study; however, we can reimburse any reasonable expenses such as travel and parking costs incurred by your participation in the study.

What are the possible risks/side effects of taking part?
MRI
MRI scans do not involve X-rays or radioactivity. There are very few risks associated with having an MRI scan. MRI scanners have been used for the past 25 years on millions of patients worldwide and are considered very safe. Some people (less than 5% or 1 in 20) experience a sense of being closed-in (claustrophobia). The MR system is noisy, but you will be provided with headphones or earplugs to wear. You will be provided with a 'squeeze-ball' alarm, which you are free to use if you feel any discomfort. The radiographer conducting the scan will be able to see you and talk with you at all times, and will stop the scan if necessary.

Cannulation
Placing a small plastic tube (cannula) into a vein can cause some discomfort and very rarely can lead to infection, but this is highly unlikely in the short time it will be in place. Some people may get bruising at the site where the cannula is inserted. This procedure is performed regularly in the hospital and is generally very safe. The cannula will be inserted just before the scan and will be removed immediately afterwards.

Fumarate injection
Although Hyperpolarised Carbon MRI is a new technology, tests up to now with pyruvate (a naturally occurring substance in the body) have demonstrated no significant safety issues. Fumarate is another naturally occurring substance in the body, so is not expected to cause any issues. Although it is unlikely that an allergic reaction or other side effect will occur, there are facilities in place within the MRI unit, and within the hospital, to manage these appropriately.

Gadolinium contrast injection
Patients might require an injection of Gadolinium (contrast agent) through their cannula. The decision whether Gadolinium might be injected will be discussed with you prior to the scan by the researcher. Gadolinium is given to patients during scans to help obtain a clear image of the inside of the body. It is known that small amounts of Gadolinium may remain in the brain after a scan with this agent, although there is currently no evidence that these small amounts cause any harm. Gadolinium is essential for diagnosing a wide range of life-threatening and debilitating diseases and continues to be widely used in a large number of clinical MRI scans. If you need a scan with Gadolinium as part of a research study, your researcher will use the lowest dose required for a clear image. If you have any questions about your scan, please speak to the research team.

Optional biopsies
Where possible, results and unused tissue from biopsies taken for clinical use or other ethically approved studies will be used in this study to reduce the number of biopsies you will have. The research team will only take the required amount of tissue for their analysis and any remaining will be kept according to standard NHS practice. Where this is not possible we may ask if an extra tissue sample can be taken at the same time point. If you are due to have surgery, we would like your permission to use some of the remaining tissue not required for your clinical diagnosis for this study. We will not attempt to obtain these biopsies more than

once on each occasion and will only perform these procedures if the doctor undertaking them assesses it to be safe to do so. You will need to indicate if you agree to this in the consent form. If any of these are not possible, we may ask if you are willing to have a separate **optional** biopsy specifically for this study. If this is the case, you will be given a separate information sheet clearly explaining the details of this separate **optional** biopsy and you will be asked to sign a separate consent form.

Discomfort and bruising may occur during and after biopsy, however most patients cope well with this. Pain relief will be available in the unlikely event that any discomfort becomes more severe. The most important side effects that you need to be aware of are:

- Bleeding which may occur at the site of biopsy and happens to 2 in 100 people (2%).
- Infection under the skin, which happens to 1 in 100 people (1%).
- Infection on the skin surface where the needle passes through, this happens to 2 in 100 people (2%)
- Where biopsies are taken but the sample collected is so small that the tumour is missed or because the sample taken of the tumour is not representative of the whole tumour. This happens to 5 in 100 people (5%).

Should any of the above occur, the appropriate medical measures will be taken to correct the issue such as antibiotic treatment for infections or closure of bleeding areas.

Other Studies

It is possible that if you are already contributing to or plan to contribute to other research studies, being part of this study may cause difficulties for you, our research and other researchers. We will try and limit these difficulties as much as possible. If you are helping on other research studies or plan to and are interested in participating in our study, please let us know, so we can discuss this and help as best we can. It is important for you to consider the time and other commitments required in participating in several studies simultaneously. We would be happy to discuss this with you and we can also talk with your family if required.

What happens at the end of the study?

The data from the images and tissue samples collected will be analysed, and the results will be used to improve our understanding of tumours and hyperpolarised imaging. Your data, images and samples collected during the study may be transferred in an anonymised way to research collaborators working in a similar field on other ethically approved studies and this may include transfer abroad or to commercial companies. These will be labelled with a participant unique study code, which will not be able to identify as coming from you. On the consent form, you will be asked to give permission for research staff to consult your medical records collected. Your identity will be kept strictly confidential.

What if there is a problem?

Any complaint about the way you have been dealt with in the study or any possible harm you might suffer will be addressed. The detailed information on this is given in Part 2.

Who will have access to the scans and results?

Any information and images collected during the study will be subject to the usual rules for medical confidentiality. Imaging data will be stored on NHS or University of Cambridge secure data storage in either partially anonymised or non-anonymised but encrypted form. Only the staff undertaking the study will have access to these non-anonymised scans and data. All images will be read by a board-certified radiologist.

Will my consultant be informed?

Your consultant will be aware of your participation in the study.

Will my GP be informed?

We will not inform anyone of your involvement in the study without your consent; however, we would recommend that you allow us to inform your General Practitioner (GP). If you do agree to this, we may contact your GP (if you are not seen in clinic) for an update on your progress at 12 months after your final research scan.

If the information in Part 1 has interested you, and you are considering taking part, please read the additional information in Part 2 before making any decision.

Part 2

What will happen if I do not want to continue with the study?
You can withdraw from the study at any time without explanation. This will not affect any investigations or examinations that you might have in the future in the course of your routine health care. We would like your permission to use the data (without any personal details attached) up to the time of your withdrawal.

What if there is a problem?
If you have concerns about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions (see contact details at the end of this information sheet).

If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. The Patient Advice and Liaison Service (PALS) are available by telephone on (01223) 216756 and email at pals@addenbrookes.nhs.uk, regarding any formal complaints about the study.

Are there compensation arrangements if something goes wrong?
In the unlikely event of something going wrong and your being harmed during the study, this is covered by NHS and professional indemnity insurance. Problems related to the study design are also covered by insurance taken out by the University of Cambridge.

How will we use information about you?
We will need to use information from you and your medical records for this research project.

This information will include your NHS number, name and contact details. People will use this information to do the research or to check your records to make sure that the research is being done properly.

People who do not need to know who you are will not be able to see your name or contact details. Your data will have a unique code number instead.

We will keep all information about you safe and secure.

Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

What are your choices about how your information is used?
You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have.

We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.

Where can you find out more about how your information is used?
You can find out more about how we use your information:

- At www.hra.nhs.uk/information-about-patients/
- For Cambridge University Hospitals NHS Foundation Trust, please visit: https://www.cuh.nhs.uk/corporate-information/about-us/our-responsibilities/looking-after-your-information, or email the Data Protection Officer at: gdpr.enquiries@addenbrookes.nhs.uk

- For University of Cambridge, please visit: https://www.medschl.cam.ac.uk/research/information-governance/, or email the Information Governance team at: researchgovernance@medschl.cam.ac.uk.

Keeping information for future research
Information about you that is collected during a research study may be kept securely to be used in future research in any disease area, including research looking at social and economic factors affecting health. This may include combining it with information about you held by other health or government organisations such as NHS Digital. Usually the information is combined together by matching information that has the same NHS number. Doing this makes maximum use of the information you have provided and allows researchers to discover more. Researchers may not be able to specify all the possible future uses of the information they keep. It could include providing the information to other researchers from NHS organisations, universities or companies developing new treatments or care. Wherever this happens it will be done under strict legal agreements. This information will not identify you and will not be combined with other information in a way that could 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.

What will happen to my samples?
All samples taken from an individual participant will be labelled with a code to allow them to be traced as coming from the same individual. These unique participant codes will be suitably anonymised so you as the participant are not identifiable, except to the core research team.

Tissue samples (e.g. biopsies) will be processed and examined by suitably trained staff and may include genetic testing. This may include but not limited to growing cells for further experiments to look at cell metabolism (this will not require your involvement) and will be destroyed appropriately after the experiments have been completed. They will not be stored indefinitely and will be stored for up to 15 years in a secure tissue storage facility before being destroyed. Blood samples will be analysed and destroyed when analysis is completed.

Some samples will be sent to third party companies or registered charities for analysis using the unique participant code, which may include sending abroad.

What will happen to the results of the study?
Study results will be analysed for the purpose of publishing the results in medical journals and findings may be presented at both national and international scientific meetings. Participant confidentiality will be maintained at all times.

If you wish, a summary of the results of the study can be communicated to you in written form. We will not be able to share individual results with you directly. Please inform the researcher that consents you to the study if you wish to receive these and provide an email address on the consent form.

Who has reviewed the study?
All research in the NHS is looked at by an independent Research Ethics Committee to protect your safety, rights, well-being and dignity. This study has been reviewed and given a favourable opinion by Essex Research Ethics Committee.

Contact details for further information

All of your questions should have been answered but if you have any further questions, you can contact the study team during office hours (9am to 5pm) who can provide further information regarding the study.

Please also contact the study team in the event of the following occurring:

- if you suffer an illness or a possible study related injury
- if you feel different in any way
- if you are admitted to hospital for any reason
- if you are seen at a casualty/accident/emergency department for any reason.

Telephone: 01223 767926
Email: radiology.research@addenbrookes.nhs.uk

Out of Hours
If you decide to participate in this study, in the event of an emergency out of office hours, please contact:

Your own GP practice's telephone number. If the practice is closed you will either be diverted to the out of hours surgery or a recorded message will provide further instructions to obtain help.

At any time

Failing to contact one of the above numbers at any time, please contact:

A&E department 01223 217118

For complaints

PALS (Patient Advice and Liaison Service):

Telephone 01223 216756
Email pals@addenbrookes.nhs.uk

Thank you for considering taking part in this study. If you require any further information, please do not hesitate to contact us, we will be pleased to help you in any way we can. A copy of the consent form will be provided for you.