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Participant Information Sheet

Study title

Molecular Imaging of Neurodegenerative Disease – Mitochondria, Associated Proteins & Synapses – Amyotrophic Lateral Sclerosis

Short Title: MIND-MAPS-ALS

Sponsor: University of Exeter

Invitation

You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this.

What is the purpose of the study?

Amyotrophic lateral sclerosis (ALS) is the most common type of motor neurone disease. It is a disease that causes the loss of the motor nerve cells that control muscle movement. This causes loss of muscle strength and increasing body weakness. The exact causes of the loss of motor nerve cells are still unknown. We know, however, that several toxic proteins collect in the brains of

people with ALS and lead to cell loss. These proteins effect many parts of the cells, especially the mitochondria. Mitochondria are the "powerhouses of cells" and their function is really important in maintaining a healthy nerve cell. Damage to the mitochondria can cause the motor nerve cells to die. We know that one of the steps before the death of the nerve cells, is the loss of synapses in the brain. Synapses are the place where each nerve cell connects with others and these structures permit a nerve cells to pass an electrical or chemical signal to each other.

Positron emission tomography (PET) of the brain is a powerful and safe scanning technique that allows us to assess the role of mitochondria and synaptic function in people with ALS using three different types of PET scan ([^{18}F]BCPP-EF, [^{11}C]SA4503, [^{11}C]UCB-J).

In this study, we aim to use PET scans to evaluate the function of mitochondria and synapses in people with a sporadic form of ALS and with a familial form (genetic) of ALS, and compare the findings with a group of healthy volunteers. We will also investigate for links between mitochondria and synaptic function and severity of symptoms in people with ALS. Our findings will provide understanding related to the cause of the disease and will help us track its progression over time. Most importantly the findings will help with the discovery of new targets for the development of treatments for ALS.

Why have I been chosen?

You have been chosen because you have a diagnosis of ALS with limb onset.

Do I have to take part?

No, it is up to you to decide whether or not to take part. If you do decide to take part, you will be given this information sheet to keep and be asked to sign a consent form. If you have agreed to

take part you are still free to withdraw at any time and this will not affect the standard of hospital care you receive. You do not have to provide a reason for dropping out. However, should you wish to provide your reason this may be useful for the management of our study.

What is involved in this study if I take part?

If you are suitable, and agree to undergo this study, we will ask you to attend the NIHR Imperial Clinical Research Facility and Invicro for clinical and imaging assessments. Both sites are located at Hammersmith Campus in West London. Invicro is a Clinical Imaging Centre located at Hammersmith Hospital Campus (Du Cane Road, W12 0NN, London), with established expertise in state-of-the-art molecular imaging techniques. Invicro provides a pleasant environment for the patients and world-class capabilities by bringing together state-of-art equipment and research methodology. In the present study, the role of Invicro is that of a research facility with no commercial interest. All appointments will be on a weekday.

Screening and clinical assessments will last up to 4 hours and will take place at the NIHR Imperial Clinical Research Facility. During this time, you will have the opportunity to discuss the study with the doctor, ask any question you may have and then, if you agree to take part into this study, you will be asked to sign the consent form. A copy of which will be given you for your records. No research related activity can take place until you have given your informed consent. We will then assess your suitability to take part in the study and we will conduct a specific neurological examination and questionnaires in order to assess the severity of your condition. Neuropsychological assessment using brief questionnaires will be performed, in order to test your memory and thinking. This data will help us to understand the relationship between system nervous damage and disease progression in ALS. We will also ask you to undertake a blood sample collection of about 50 mL in total (around 3 tablespoons). About 20 mL will be used to

assess the biochemical parameters, any bleeding disorders, and for a pregnancy test (if you are a woman of childbearing potential). About 30 mL will be processed for analysis of biomarkers and for storage. We will ship a part of the processed blood sample to a laboratory located in the United States, specialized in the analysis of some substances (called biomarkers), that are altered in ALS and in other neurological diseases. We will store the rest of the samples in biobanks for future analysis as part of Ethically approved research studies, in case of any new relevant discovery in the field of ALS (please read the section "analysis and storage of the samples" below.

We will then ask you to undertake three PET scans at Invicro. A PET scan is special type of scan, which can be used to measure chemical changes within the brain. Each imaging visit may take around 4 hours or longer (though we will do our best to make it as short as possible). Before the scan we will need to place two needles: one into a vein and one into an artery in your arm. Arterial cannula is needed to collect a small amount of blood (around 132 mL in total or about 9 tablespoons during the PET scan for aiding with the analysis of the data. It will be performed by an experienced anesthetist doctor. Prior to inserting a needle into the artery, blood sampling and a medical test (Allen's test) for evaluating the blood flow in the arm will be performed. Women of child bearing potential will undergo a urine pregnancy test. Each PET scan will take about 1.5 hours. During this time you will be asked to lie on your back on a bed with your head resting in the scanner. The tracer injection will not cause any discomfort; no immediate side effects have been reported in humans studies with the tracers used in the present study. During each PET scan you will also be asked to undertake up to two low dose brain CT scans, which are necessary to measure data from the PET scan. We will ask you to fast 3-4 hours prior to the PET scan. Refreshments will be offered after the PET scan. We will ask you to bring with you your medications because they can be taken once the PET scan has been completed.

We will ask everyone to have a magnetic resonance scan (MRI). MRI is a special scan, which gives a detailed structural picture of the brain and does not involve any additional radiation. It is used to help with PET analysis. This scan usually lasts about 1.5 hours (but may take a little longer, if you need time to settle in comfortably).

We will be ask participants to undertake a 6-month and 12-month (+/- 4 months) follow-up a clinical and neuropsychological assessment visit and a repeat MRI and PET scan (only [^{11}C]UCB-J). Clinical assessment and scans will be performed in the same way indicated above. If you experience any distress during the study, we will endeavor to provide you with any support you may require.

VISIT 1: Screening, Clinical and Neuropsychological assessments, Blood Sample Study time point: baseline Time: up to 2-4 hours Location: NIHR Imperial Clinical Research Facility, Imperial College Healthcare NHS Trust, Hammersmith Hospital W12 0HS	Clinical assessment consists of a brief medical history and examination and the completion of 9 scales that assess the severity of the disease symptoms as well as mood, sleep, pain and other symptoms. Neuropsychological assessment will consist of 3 questionnaires that will assess memory and thinking. Blood sample collection for safety and biomarkers/storage will be performed by a research nurse (about 20 mL for safety tests and about 30 mL for biomarker analysis)

	We will also collect vital signs such as blood pressure and heart rate. Blood pregnancy test (in women of childbearing potential)
VISIT 2: MRI and PET scans Study time point: baseline Time: 4-5 hours Location: Invicro London, Du Cane Rd, White City, W12 0NN	On scan day we will perform a urine pregnancy test if needed. Then the anesthetist will perform an Allen's test to check the blood supply of your arm (it consist just in putting some pressure on the wrist and it lasts a few seconds). Vital signs before and after PET scans will be collected. Intravenous and arterial cannulations will be placed. [^{18}F]BCPP-EF PET scan (approximately 1.5 hours with collection of around 132 mL of blood for PET analysis) MRI scan (approximately 1.5 hour)
VISIT 3: 2 PET scans Study time point: baseline Time: 4-5 hours	Urine pregnancy test if needed Allen's test Vital signs before and after PET scan Intravenous and arterial cannulation

Location: Invicro London, Du Cane Rd, White City, W12 0NN	[^{11}C]SA4503 PET scan (approximately 1.5 hours, with collection of around 132 mL of blood for PET analysis) [^{11}C]UCB-J PET scan (approximately 1.5 hour with collection of around 132 mL of blood for PET analysis)
VISIT 4: Clinical and neuropsychological assessments, blood Sample Study time point: 6-months follow-up Time: 2-3 hours Location: NIHR Imperial Clinical Research Facility, Imperial College Healthcare NHS Trust, Hammersmith Hospital W12 0HS	Clinical and neuropsychological assessment Blood sample for safety and biomarkers/storage (about 20 mL for safety tests and about 30 mL for biomarker analysis). Vital signs collection
VISIT 5: MRI and PET scan Study time point: 6-months follow-up Time: 4-5 hours Location: Invicro London, Du Cane Rd, White City, W12 0NN	Urine pregnancy test if needed Allen's test Vital signs before and after PET scan Intravenous and arterial cannulation [^{11}C]UCB-J PET scan (approximately 1.5 hour with collection of around 132 mL of blood for PET analysis) MRI scan (approximately 1.5 hour)
VISIT 6: Clinical and neuropsychological assessments, blood sample	Clinical and neuropsychological assessment

Study time point: 12-months follow-up (+/- 4 months) Time: 2-3 hours Location: NIHR Imperial Clinical Research Facility, Imperial College Healthcare NHS Trust, Hammersmith Hospital W12 0HS	Blood sample for safety and biomarkers/storage (about 20 mL for safety tests and about 30 mL for biomarker analysis). Vital signs collection
VISIT 7: MRI and PET scan Study time point: 12-months follow-up (+/- 4 months) Time: 4-5 hours Location: Invicro London, Du Cane Rd, White City, W12 0NN	Urine pregnancy test if needed Allen's test Vital signs pre and post PET scan Intravenous and arterial cannulation [^{11}C]UCB-J PET scan (approximately 1.5 hour with collection of around 132 mL of blood for PET analysis) MRI scan (approximately 1.5 hour)

The PET tracer will be produced at Invicro the day of the PET scan. If we have problem with the production of the PET tracer, or other circumstances, additional visits to Invicro may be arranged. MRI may be performed before the PET scan and the order of the PET scans may change, if needed. The order of visit may be changed, based on availability and participant convenience.

We will reimburse transportation to and from home to the hospital and refreshments throughout your visit. Please keep any travel tickets or parking receipts. You will need to provide those to the research team in order to receive a refund. We will also offer a thank you of £250 per scan (up to £2,000) as remuneration for your time-commitment and inconvenience and a further £150 per visit (up to £1,200) for your care-giver/companion.

Medication restrictions: There are some medications, which have the potential of effecting the PET scan results. Therefore certain medications must be stopped prior to PET measurements as follows: (a) For [^{18}F]BCPP-EF PET: **metformin** and **non-steroidal anti-inflammatory drugs such as aspirin, indomethacin, diclofenac, piroxicam** and **ibuprofen** must be stopped at least 4 days prior to the PET scan; (b) For [^{11}C]SA4503 PET: steroids such as **dehydroepiandrosterone, progesterone, pregnenolone, testosterone** and **deoxycorticosterone** must be stopped at least 4 days prior to the PET scan, and **haloperidol, fluvoxamine** and **donepezil** must be stopped at least 7 days prior to PET measurement; (c) [^{11}C]UCB-J PET: **levetiracetam** and **bevetiracetam** must be stopped at least 7 days prior to the PET scan. If any of these treatments are essential for your clinical management, you will be excluded from the study.

Analysis and storage of the samples

During this study we will collect blood and urine samples for analysis and for storage. The analysis we make for safety (laboratory tests, urine analysis) will be conducted in the laboratory of analysis of the NIHR Imperial Clinical Research Facility. The blood collected to measure the levels in the blood of the biomarkers will be temporarily stored at Invicro and then shipped to a laboratory located in the United States.

With your permission, a part of the blood collected will be stored, equally split, in two biobanks where they will be safely kept indefinitely. One biobank is located at University of Exeter and is owned by the research group. The other one is located in Indianapolis, USA, and is owned by Azenta Life Sciences, a company specialized in storing research samples from all over the world. The contact for AzentaLife Sciences isJenny Then. You can contact Jenny.then@azenta.com if you wish to know more about the storage of samples in the biobank. The samples will be stored in a way in which it will be impossible to trace back to the donor. We will also ask your permission

to re-analyze the samples, as part of future ethically approved research, in case of new discoveries in ALS in the future. More detailed information is contained in the section: "Will my taking part in this study be kept confidential?" below.

What are the possible risks of taking part?

Blood sampling

This will be performed by experienced nurses and is low risk. Occasionally, you experience minor discomfort or have a bruise after the procedure. Any unexpected results on your blood tests, when clinically relevant according to the study physician, will be reported to your GP with your permission.

Cannulation

Insertion of a cannula into a vein or artery may cause brief discomfort as the cannula enters the skin, similar to the discomfort you have when having an injection. To insert the cannula into your artery we will use a local anaesthetic to numb the area so you do not feel pain. Detailed instructions on insertion of the arterial line and the care of the site after removal of the arterial line are provided by the study doctors. Risks of any cannulation include minor local bleeding and bruising. Very rarely, a blood clot could form around the cannula. Most people have no after-effects of cannulation. However, occasionally, a scar may occur. Even when this happens, the scar left over the long term usually is small.

More rarely, there can be some discomfort lingering after the cannula insertion. The full list of potential complications is as follows:

Common complications:

· Temporary artery spasm (19.7%)

· Bruising (14.4%)

Less common complications:

- Localised site infection (0.72%)
- Bleeding (0.53%)
- Generalised infection (0.13%)
- Damage to the fingers due to inadequate blood supply (0.09%)

Rare complications:

- Paralysis of median nerve (runs from the forearm into the palm of the hand) (<0.1%)
- Air embolism (air bubble trapped in a blood vessel. When an air bubble travels along an artery, it moves through a system of blood vessels that gradually become narrower. At some point, the embolus will block a small artery and cut off the blood supply to a particular area of the body.) (<0.1%)
- Carpal tunnel syndrome (median nerve becomes pressed or squeezed at the wrist causing pain, weakness, or numbness in the hand and wrist) (<0.1%)

Most arterial cannula insertions are done without any problem. You may notice bruising around the area where the cannula was inserted, which should disappear after a week or two. The place where the cannula was inserted will heal quickly within a few weeks, with any marks fading with time. Participants should avoid physical exercise or heavy lifting for 24 hours after removal of the arterial line

If any of the following occur within 72 hours after the cannula was removed, you MUST consult the study doctor immediately.

- Intense or sharp thumb or palm pain
- If anywhere on your hand, fingers or thumb appears pale and cold or
- If anywhere on skin to the hand, fingers or thumb appears dark or blackened and cold
- If you notice an unusual ‘lump or bump’ over where the cannula was inserted
- If you develop a fever (raised temperature) and feel unwell

· If you feel a sudden shortness of breath

· The dressing becomes soaked with blood (If you experience heavy bleeding), apply firm pressure to the area with the dressing supplied for 5 minutes and attend Accident & Emergency for advice/ treatment. Please also notify the Study Doctor.

Imaging procedures

The administration of [^{18}F]BCPP-EF, [^{11}C]SA4503 and [^{11}C]UCB-J, as well as the low dose head computed tomography (CT) scans that we need to perform with the PET in order to obtain a better imaging, will expose you to a maximum of 9.94 mSv of ionising radiation. Exposure to 9.94 mSv of additional annual ionising radiation is equivalent to 3.7 years of annual ionizing radiation exposure (2.7 mSv per year) for an average UK resident. The additional risk of developing a fatal cancer associated with this exposure has been estimated to be about 1 in 2000 in a healthy 40-year-old subject. The overall UK cancer mortality rate of about 1 in 3.5, and therefore the additional risk due to participation in this study is very low. Along with other procedures involving radiation (including X-rays), PET scans can be hazardous to an unborn child. If you are a woman of childbearing age you should not take part in the study unless you are on a reliable form of contraception, and even if this is the case a urine pregnancy test prior to the PET scan will be performed.

The MRI scan does not expose you to ionising radiation, but it can be noisy (we can provide you with earplugs to counter this). An MRI is a very strong magnet, so if you think you may have any metal in your body (e.g. as a result of surgery, or an accident, such as metal filings in your eye due to welding accidents) you must let us know, so we can assess if the procedure will pose any risk to you. There is otherwise no discomfort associated with MRI scanning, other than having to lie on your back and try to remain as motionless as you can for about 90 minutes. However, if you

are claustrophobic you may find MRI difficult to tolerate, if so please let us know in advance. Some of the MRI sequences, called diffusion imaging, functional imaging (fMRI) and arterial spin labelling (ASL), are used to take detailed pictures of the brain and of some functional aspects (how it works). These, however, are sequences that are not used as standard by the imaging facility (Invicro) and are acquired by another supplier, as part of an agreement between the imaging facility, the suppliers, and the providers of the softwares. This could mean we will be using the MRI scanner in a different way to what is standard (we call it "off-label"). The use of these sequences has the purpose of accelerating the rate at which the scanner can acquire data, thus reducing scan time, improving the subjects' experience, reducing motion disturbance (called artefacts), and producing better-quality image data.

You should be aware that the scans used in this study might reveal an unexpected fact about you that may have relevance for your health. In the unlikely event of this happening, we will discuss this with you and, if necessary, provide any support that you may require, such as arranging follow-up tests and/or treatment and informing your GP.

What are the possible benefits of taking part?

PET scans are not a form of treatment and do not provide any direct benefits to you. However, the knowledge acquired from this study will improve our understanding of ALS and may help us to provide the means for the development of better drugs for this disease.

What if something goes wrong?

The University of Exeter has insurance cover in place to cover its legal liability for injury or illness arising from this study. If you are following a private insurance scheme, you should notify your insurer that you are taking part in this study. If you are harmed due to someone's negligence, then

you may have grounds for a legal action. In case you are harmed due to negligence during or as consequence of procedures carried out by NHS staff, for example because of blood sample collection, NHS indemnity scheme will apply.

Will my taking part in this study be kept confidential?

The University of Exeter is sponsor for this study based in the United Kingdom. We will be using information from you and your medical records in order to undertake this study and will act as the data processor for this study. This means that we are responsible for looking after your information and using it properly.

In 2018 regulatory changes in the way that data is processed came into force, with the EU General Data Protection Regulation 2018 (GDPR) and the Data Protection Act 2018 (DPA 2018). Since the UK left the EU, the key principles of EU GDPR have been adopted in the UK GDPR (a 'UK-only' version) and the DPA 2018 still applies.

The University of Exeter terms its lawful basis to process personal data for the purposes of carrying out research as being in the 'public interest'. The University continues to be transparent about its processing of your personal data and the participant information sheet should provide a clear explanation of how your data will be collected, processed, stored and destroyed. If you have any queries about the University's processing of your personal data that cannot be resolved by the research team, further information can be obtained from the University of Exeter's Data Protection Officer via the link; https://www.exeter.ac.uk/aboutoursite/dataprotection/dpo/

If you have any concerns about how your data is controlled and managed for this study, then please contact the Sponsor Representative: Pam Baxter, Research Governance Manager (Contact details at the end of the information sheet).

There are two possible scenarios

(1) Enrolment from NHS clinic: patients enrolled at the Royal Devon & Exeter NHS Foundation Trust (RD&E), where the identifiable information will be transferred to the University of Exeter

(2) Enrolment from non-NHS source: Patient enrolled at the University of Exeter, where the identifiable information will not be transferred to the RD&E Trust.

The University of Exeter will use your name and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Individuals from the University of Exeter or regulatory authorities may look at your medical and research records to check the accuracy of the research study, where it is relevant to you taking part in the research. The RD&E Trust will securely pass these details to the University of Exeter along with the information collected from you. The only people at the University of Exeter who will have access to information that identifies you, will be people who need to contact you regarding the research study or to 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 or contact details.

The Imperial Clinical Research Facility is part of Imperial College Healthcare NHS Trust, and we rely on several NHS systems and procedures to support our research. To include you in a study we need to record information in your medical healthcare record, whether you are a patient or a healthy volunteer.

Healthcare records may be in paper or electronic format and will typically include laboratory test results, radiological imaging (e.g. ultrasound scans, X-rays, MRI etc), clinical notes, routine observations, prescription charts (a list of medicines given to you) and other study-specific information which is collected as part of the research. Such information may be valuable to

support your normal health care now, or in the future. If you are not already an NHS Trust patient, we will need to register you.

Although information collected as part of this study will be available in your medical records, a duty of confidentiality applies, and staff within the NHS may only access your records if they have a legitimate and lawful reason to do so. If you have any concerns about this, please speak with your study doctor.

All information collected in this study will be kept strictly confidential and stored either on an encrypted password protected computer, or in a locked cabinet in a secure office at the University of Exeter, which can only be accessed by the research team. You will be allocated a unique participant number, to ensure your information will be protected and cannot be identified outside of the research team. Any personally identifiable information will be stored separately and securely from information obtained from the research, it will only be kept for 10 years after the study has finished and securely destroyed at the end of the 10 years.

Your rights to access, to 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 study, 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.

The University of Exeter will keep identifiable information about you from this study for 10 years after the study has finished. We will use this information for research purposes only.

Referral forms containing name, date of birth and address will be sent to Invicro London through an encrypted process in order to correctly identify you prior to your scans.

If you consent to take part in the research, with your permission we will write to your GP to inform him/her that you are participating in this study.

You can find out more about how we use your information by contacting the Chief investigator Prof. Marios Politis (m.politis@exeter.ac.uk) or the study team:

Study Doctor

Dr Edoardo De Natale_____ Tel: 07503 741242 Email: e.de-natale@exeter.ac.uk

Study Coordinator:

Name: Martin Howard_____ Tel: 01392 723 037 Email: M.howard@exeter.ac.uk

All employees working in the NHS are bound by a legal duty of confidence to protect personal information and therefore any information you give during this study will be kept confidential. Should we be concerned about your health or wellbeing we may discuss this with your clinical care team/GP.

Data collected during your participation in this research project may also be stored electronically on a secure research PET database at the University of Exeter and Invicro London and may be used in the future by both Invicro London and the University of Exeter to compare with results from other studies. However, such data will be anonymised so that you cannot be identified on the database. All stored data will comply with the provisions of the UK General Data Protection Regulation (UK-GDPR), and of the Data Protection Act 2018 and will only be accessible via written permission of the Chief investigator of this study. Your anonymised data may be used in future ethically approved research studies, we will ask for your consent for this. The 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. It will not be used to make decisions about future services available to you, such as insurance.

What will happen to the results of the research study?

The results of the research are likely to be published in a peer-reviewed scientific journal. You will not be identified in any report/publication.

If you wish, feedback will be sent to you from the research doctor with the results, which will be in a manner understandable to a non-medical person.

Who is organising and funding the research?

The study is funded by Invicro and University of Exeter is the sponsor of the study.

This study is part of a collaboration called MIND MAPS between Invicro, University of Exeter, London and Imperial College, London to develop better ways of imaging neurodegenerative disease. The results of all studies in the MIND MAPS collaboration are going to be shared between all the participants and published in scientific journals.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given a favourable opinion by the London - Bromley Ethics Committee. This study has also been reviewed and approved by the NHS Health Research Authority (HRA) and the Administration of Radioactive Substances Advisory Committee (ARSAC).

Contact for Further Information

If you have any questions or there is anything you wish to discuss please contact the Chief Investigator Prof. Marios Politis (m.politis@exeter.ac.uk) or the study team:

Study Doctor

Dr Edoardo De Natale_____ Tel: 07503 741242 Email: e.de-natale@exeter.ac.uk

Study Coordinator:

Name: Holly Wright_____ Tel: 01392 722935 Email: h.wright19@exeter.ac.uk

Sponsor Representative:

Ms Pam Baxter

Research Governance Manager

University of Exeter

Research Ethics and Governance Office, Lafrowda House, St Germans Road, Exeter, Devon, EX4 6TL Tel: 01392 723588

http://www.exeter.ac.uk/cgr/researchethics/

The study team is located at the London Offices, University of Exeter College of Medicine and Health, Translation and Innovation Hub, Central Working 4th Floor, 84 Wood Lane, White City, London, W12 0BZ.

If you agree to participate in this study, please sign the consent form. You will be given a copy of the information sheet and a signed consent form to keep for your records.