Participant Information Sheet for Patients

Study title

Molecular Imaging of Synaptic Loss in Multiple System Atrophy (MSA)

Short Title: Synaptic Loss in MSA

Chief Investigator: Prof Marios Politis

Sponsor: University of Exeter

Invitation

You are invited to take part in a research study. Your carer will also be invited to take part in a small part of this research study. A separate participant information sheet for carers will be provided to your carer. If you do not have a carer, or if your carer does not wish to take part in the study, you are still invited to participate in this study.

Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take your time to read the following information carefully and discuss it with others if you wish. If anything is unclear or if you would like more information, please get in touch with one of the study team. Take your time to decide whether or not you wish to take part.

Thank you for reading this.

What is the purpose of the study?

Multiple System Atrophy (MSA) is a chronic neurological condition that progresses over time. MSA causes symptoms such as slowness of movement and stiffness, lack of muscle control or coordination of voluntary movements, and urinary problems (dysfunction). Patients with MSA

are found to have a build-up of a protein, called alpha-synuclein, in several areas of their brain. This protein collects close to the brain cells, which provide support and insulation to nerve cells (neurons). The exact way (mechanism) that alpha-synuclein accumulation leads to the gradual breakdown of neurons, causing the symptoms of the disease, is still unclear. However, we know that even before these cells die there is a loss of synapses (the structure which allows brain cells to send messages to other brain cells and across the brain) and a decrease in the metabolism of glucose (sugar), which is used as a measure of brain activity. By use of a special scan, called Positron Emission Tomography (PET), it is possible to determine the loss of synapses (synaptic loss) and the decrease of glucose metabolism. We can do this by the use of very small amounts of radioactive substances called tracers, which are injected through a cannula (tiny tube) into your vein, the tracers attach themselves to specific targets in the brain that we wish to study. Then by using another brain scan called Magnetic Resonance Imaging (MRI) it is possible to measure brain structures and the integrity of connections (how well the connections work) between different areas in the brain.

In this study, we aim to use PET imaging specific for measuring synapses and glucose metabolism, to investigate their role in disease progression in people with MSA. We will also use PET imaging to visualize a protein called tau. Tau is a protein which builds up in a number of neurological disease, particularly in a disorder called Progressive Supranuclear Palsy (PSP), which is very similar to MSA so that it is difficult to distinguish on the basis of the symptoms alone. We expect that a group of patients with MSA will not show any sign of retention of tau in the brain, whereas we expect the patients with PSP will do. This would help having one means to distinguish these two disorders. We will also use MRI imaging to evaluate the structural and functional changes in the brain in patients with MSA. Furthermore, we will

explore the relationship between synaptic loss, glucose metabolism, and clinical features in people with MSA. Our findings will provide a deeper understanding of the brain changes specific for the disease, which will help us track the progression of MSA. More importantly, this study will help with the discovery and development of new medications aiming to delay progression of symptoms caused by MSA.

Why have I been invited?

You have been asked to participate because you are a patient that has been found to have MSA.

For this study, we intend to enrol 20 participants with this condition. This would allow us to gain significant information about the mechanisms underlying this disease. This research will take place in London. If you are not from London, travel and (in case it is necessary), accommodation will be arranged for you and your carer by the research team.

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 without giving any reasons and this will not affect the standard of hospital care you receive or your legal rights. Any identifiable data or tissue that has been already collected with consent would be retained and used in the study. No further data or tissue would be collected or any other research procedures carried out.

What is involved in this study if I take part?

If you have the symptoms that we are researching and agree to take part in this study, there are a few things we would like you to consider please. We will ask you to attend the Imperial

College Clinical Research Facility at Hammersmith Hospital, and Invicro London for the clinical and imaging assessments to be undertaken. The Imperial College Clinical Research Facility at Hammersmith Hospital Campus (Du Cane Road, W12 0NN, London), provides comfortable clinical accommodation for study participants, covering both long-term in-house monitoring as well as day visits. It is equipped to cater for research studies from across the range of medical disciplines. Invicro is a Clinical Imaging Centre located at Hammersmith Hospital Campus in West 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 London is that of a research facility with no commercial interest.

All appointments will be arranged on a weekday. All transportations to and from the research site, for you and a companion, if needed, will be arranged by us.

Before each study visit, we will ask you to withdraw the medications you take for MSA from the night before, to ensure that the data we collect are not affected by the medications. Temporary withdrawing the medications is not risky. You may feel that your movements may be temporarily worse than usual. You can take your medications as soon as the study procedures have finished. For one of the measurements it may be necessary for you to fast in the morning of the scan (i.e. not having breakfast before the scan), although we will provide you with more information about this.

Taking part will involve up to four (4) visits at the baseline of starting the study and then up to four (4) visits after 12-14 months (follow-up visits).

Details of what will happen at each visit is outlined below.

Visit 1: Screening and clinical assessment, blood and urine collection.

At the first visit the screening and clinical assessments that are required for the study will last approximately 3 hours and will take place at the NIHR Imperial Clinical Research Facility in London.

During this time, you will firstly have the opportunity to discuss the study with the doctor, ask any questions 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 to you for your records. No research-related activity can take place until you have given your written informed consent.

We will then assess your suitability to take part in the study and we will conduct a specific neurological examination. We will administer scales (questionnaires and tests) to assess the presence of symptoms related to how you move (motor symptoms), think (cognitive symptoms), and behave (symptoms related to mood, sleep, and quality of life). Some of these tests are devised as self-administration scales (i.e. you will be asked to complete these questions yourself) and some, such as the Hamilton Depression Rating Scale which assesses your mood, are structured interviews (i.e. the study doctor will ask you to reply to specific questions). For two of these questionnaires we will collect information from both you and from your carer (if they independently consent to taking part in the study). These questionnaires assess whether some motor symptoms and non-motor symptoms are present and, if so, to what degree. Collecting information from your carer allows us to collect more precise information. Each scale is a short scale composed of a few questions and takes a few minutes to complete. We will administer eleven questionnaires and five computerised tests on a tablet (notebook computer) called CANTAB which assess memory and attention.

We will also check your blood pressure, heart rate, and take an electrocardiogram (ECG) recording of your heart. We will ask you to provide a blood sample to assess for any bleeding disorders and to measure biomarkers (a type of blood test that indicates level of disease or processes) of MSA, and pregnancy test but only if you are a woman of childbearing potential. The amount of blood that will be taken will be about 60 ml or 12 teaspoons (1teaspoon = 4.92 mls). We will also ask you to provide a urine sample for chemical analysis.

All clinical assessments will be performed by a qualified doctor with previous clinical and research experience on MSA. All the equipment (computers, laptops), will be provided by the funders of the study.

Visit 2: PET Scan (and MRI).

The second visit will take place at Invicro London. In this visit you will undergo one PET scan (either with administration of the radioactive substance tracer called [^{11}C]UCB-J (which studies the loss of the synapses (junction between the nerve cells)) or [^{18}F]FDG (which studies the chemical processes that occur (metabolism) in the brain) and/or, an MRI scan. This visit will last in total about 3.5 to 5 hours, depending on whether the MRI scan is performed. In case we perform the [^{18}F]FDG PET, you will be advised in advance, as you will need to withdraw food from the night before (i.e. you will not have any breakfast). When you arrive we will first check whether you have suffered any adverse event (AE) since your first visit, check your blood pressure, and heart rate, and check the blood levels of glucose (if the [^{18}F]FDG PET scan is performed). Then we will insert the venous cannula in one arm, for the injection of the tracer.

If in this visit you will undergo the [^{11}C]UCB-J PET scan, another needle will need to be placed into an artery in your wrist. This cannula is needed to collect a small amount of blood during the PET scan (around 12 teaspoons). This is needed to help in the analysis of the research data of the PET scan. We will then perform a short and simple medical test called Allen's test, which allows us to assess the blood flow in the arteries of your arms. It involves you firstly clenching your hand into a fist, then pressure will be applied to your wrist and then you can relax your hand. It enables the blood flow to be assessed by the researcher and then the pressure can be released. Each PET scan will take about 2 hours to perform. During this time, you will be asked to lie on your back on a bed with your head resting in the scanner. One member of the staff will always be available to assist you in case you need anything. The MRI scan does not involve the need for any placement of a cannula into your vein. For the MRI exam, you will be asked to lie back on a bed during the duration of the scan. The total duration of the scan is of about 1.5 hours. For your comfort, the scan will be split into two sessions of around 45 minutes each, with an optional 30-minute break in between and we will ask some questions for safety reasons before we perform the MRI scan. One member of the staff will always be available in another room to assist you throughout the duration of the exam.

The tracer injection that is used for the PET scan should not cause any discomfort to you and no side effects have been reported from human studies that have used the same tracers injected in the present study. Immediately before a short low dose CT scan will be performed. This is necessary to measure the data from the PET scan (e.g. to understand if the head has moved during the PET scan). Rarely, if the head has moved, there may be the need to repeat the CT at the end of the PET scan.

You will be offered refreshments after the PET scans.

Visit 3: PET Scan (and MRI).

The third visit will take place at Invicro London. In this visit you will undergo one PET scan (either with administration of [^{11}C]UCB-J or [^{18}F]FDG) and/or, an MRI scan, if this has not been performed during the visit 2 as detailed above. This visit will last in total about 3.5 to 5 hours, depending on whether the MRI scan is performed, as described above in visit 2. The procedures and the way that they take place will be the same as in visit 2. A group of 10 consecutively enrolled participants with MSA will undergo a PET scan using a different tracer called [^{18}F]APN-1607, which is sensitive for the protein tau in the brain. The procedures for the PET scan with [^{18}F]APN-1607 would be the same as for the scan with [^{11}C]UCB-J. In case you will belong to the group of 10 MSA participants, you will not be able to choose if you receive [^{18}F]APN-1607 or [^{11}C]UCB-J.

You will be offered refreshments after the PET scans.

Visit 4: Cerebrospinal Fluid Collection – Optional part of the study

The fourth visit is an optional part of the study and if you choose to take part then Visit 4 will take place in the Imperial Clinical Research Facility. This visit will last about 1.5 hours, with up to two hours extra time allowed for monitoring for any side effect from the lumbar puncture procedure. We will collect cerebrospinal fluid (CSF) using a technique known as lumbar puncture. CSF samples will be used to measure biomarkers of the disease (a biomarker is a measurable indicator of disease state). Lumbar puncture is a common procedure in both the clinical and research setting. Your consent for undergoing this procedure is optional and your decline does not preclude your participation in the study. If you decline to undergo this procedure, this visit will not take place.

Lumbar puncture, also known as a 'spinal tap', is a minor procedure where a small needle is used to withdraw about CSF from the base of the spine. It takes about 15 minutes and is done under local anaesthetic which numbs the area. You will be asked to lie on your side and curl up as tightly as you can. After cleaning the skin of the lower back, local anaesthetic is injected to make the area go numb. This will sting for a couple of minutes, and then the skin will go numb. A needle is then used to collect 2 tablespoons (15-20 mL) of CSF. You will stay in the private ward of the Imperial Clinical Research Facility for half a day from 8:30am until midday after the procedure; and then, if there is no side effect, you will be able to go home. We will contact you by phone around 7 to 10 days following the procedure to make sure that you are feeling OK.

Visit 5: Follow-up clinical assessment. Blood and urine collection

For Visit 5 we will ask you to come again after 12-14 months, to repeat the clinical assessment., the blood and urine collection. The procedures will be the same as in visit 1.

Visit 6: Follow-up PET scan (and MRI scan)

For Visit 6 we will ask to repeat the PET scan (with administration of either [^{11}C]UCB-J or [^{18}F]FDG) and/or, an MRI scan). The procedures will be the same as detailed above in visit 2.

Visit 7: Follow-up PET scan (and MRI scan)

We will ask you to repeat the PET scan (with administration of either [^{11}C]UCB-J or [^{18}F]FDG) and/or, an MRI scan, if not performed during visit 6). The procedures will be the same as in visit 3. If you have been enrolled to perform the [^{18}F]APN-1607 PET scan and you performed it during the baseline assessment, you will not need to perform it a second time. If you have

been enrolled to perform the [^{18}F]APN-1607 PET scan and you have not performed it during the baseline assessment, you will perform it at this time point.

Visit 8: Follow-up Cerebrospinal Fluid Collection Optional part of the study

For Visit 8 and if you agreed to the optional part of the study to obtain a CSF sample, then we will ask if we could repeat the Lumbar Puncture (spinal tap) for the collection of an additional sample of CSF. The procedure will be the same as in visit 4. This procedure is optional.

The study visits will then be completed.

Please note:

You can contact the study team at any time if you have any questions which arise in between the study visits. You can find the contacts of the study team at the bottom of this document if you need to contact us.

If you experience any distress during the study, we will endeavour to provide you the support you may require.

Please find below a summary of the study visits for this study.

Summary of Visits (Baseline)

Visit 1 (Imperial Clinical Research Facility)	**Visit 2 (Scan Visit A) (Invicro)**	**Visit 3 (Scan Visit B) (Invicro)**	**Visit 4 (Imperial Clinical Research Facility)**
- Screening and clinical assessments, questionnaires, digital	- Urine sample for pregnancy test (where it applies);	- Urine sample for pregnancy test (where it applies);	- Vital signs - Lumbar puncture for CSF assessments

assessment (about 3 hours); - Blood sample for laboratory tests and pregnancy test (where it applies) (up to 15 minutes); - Urine sample	- Allen's test; - Vital signs pre and post PET scan; - Intravenous and arterial cannulation; - [^{11}C]UCB-J PET scan or [^{18}F]FDG PET scan (approximately 2 hours); or (if enrolled in this subgroup): - [^{18}F]APN-1607 PET scan (approximately 2 hours) - MRI scan (approximately 1.5 hour)	- Allen's test; - Vital signs pre and post PET scan; - Intravenous and arterial cannulation; - [^{11}C]UCB-J PET scan or [^{18}F]FDG PET scan (approximately 2 hours); or (if enrolled in this subgroup): - [^{18}F]APN-1607 PET scan (approximately 2 hours) - MRI scan, if not performed at Visit 2 (approximately 1.5 hour)	(approximately 1.5 hours)

Summary of Visit (Follow-up – approximately 1 year later)

Visit 5 (Imperial Clinical Research Facility)	**Visit 6 (Scan Visit A) (Invicro)**	**Visit 7 (Scan Visit B) (Invicro)**	**Visit 8 (Imperial Clinical Research Facility)**
- Clinical assessment, questionnaires, digital	- Urine sample for pregnancy test (where it applies);	- Urine sample for pregnancy test (where it applies);	- Vital signs - Lumbar puncture for CSF assessments

assessments (about 3 hours); - Blood sample for laboratory test and pregnancy test (where it applies) (up to 15 minutes); - Urine sample	- Allen's test; - Vital signs pre and post PET scan; - Intravenous and arterial cannulation; - [^{11}C]UCB-J PET scan or [^{18}F]FDG PET scan (approximately 2 hours); or (if enrolled in this subgroup and the scan has not been performed at baseline): - [^{18}F]APN-1607 PET scan (approximately 2 hours) - MRI scan (approximately 1.5 hour)	- Allen's test; - Vital signs pre and post PET scan; - Intravenous and arterial cannulation; - [^{11}C]UCB-J PET scan or [^{18}F]FDG PET scan (approximately 2 hours); or (if enrolled in this subgroup and the scan has not been performed at baseline): - [^{18}F]APN-1607 PET scan (approximately 2 hours) - MRI scan, if not performed at Visit 2 (approximately 1.5 hour)	(approximately 1.5 hours)

The [^{11}C]UCB-J and [^{18}F]APN-1607 PET tracers will be produced at Invicro London the day of the PET scan, although when the [^{18}F]FDG tracer is used, the study team buy it in. If for some unforeseen reason there is a problem with the production of the PET tracer that is planned to be used at the visit; or other circumstances that may arise, then you may be asked to attend

an additional visit at Invicro London. If this occurs it will be fine for the MRI to be performed before the PET scan and it will mean that the order of the PET scans may change, if needed.

A part of the blood and CSF samples for the biomarker analysis will first be transferred from the Imperial Clinical Research Facility to Invicro and then shipped to a sample storage facility located outside UK, in the United States, for analysis and storage for future research related to Multiple System Atrophy. Another part will be stored for biobanking in a sample storage facility located at University of Exeter, Devon, in the South West of England. Your sample will be coded to protect your identity and confidentiality before it is moved to any other location mentioned.

We will reimburse transportation to and from home to the hospital for you and a companion, if needed, including if asked to attend additional visits (should a problem occur with the tracer used in the PET scan). You will be provided with refreshments throughout your visits. Please keep any travel tickets or parking receipts, as you will need to provide those to the research team in order to receive a refund. We will also offer a small thank you of £400 after completion of the baseline visits and an additional £400 after completion of the follow up visits. All payments will be assessable for tax and benefits.

Incidental findings:

You should be aware that the scans used in this study might identify a previously undiagnosed illness or detect something which is abnormal and potentially clinically significant (known as an 'incidental finding'). In the unlikely event of this happening, we would inform you as soon as possible and discuss the implications and options available.

With your consent we may refer you back to your GP or another clinician for follow-up if appropriate. As a result of incidental findings you might need to be withdrawn from the research study, but we would discuss this with you.

If a possible growth is detected, your images will be referred to and reviewed by a multi-disciplinary team of experts from Imperial College Healthcare NHS Trust, who will endeavour to provide a diagnosis and if necessary recommend a plan for treatment. This is done automatically to ensure that any findings are dealt with as quickly as possible and may happen within Imperial College Healthcare NHS Trust before we have been able to contact you.

It is important to us that you are fully informed, so that you can make decisions for yourself about taking part in research at the ICRF. We will do our best to communicate with you openly and clearly, so please ask questions at any time if there is anything that you're unsure about.

Medication restrictions: We will ask you about your current and previous medications as there are some medications that should not be taken before the PET scans, as they can affect the results. Medications or supplements with known action on SV2A, such as levetiracetam and brivaracetam, must be discontinued at least 7 days prior to PET measurement. If any of these treatments are essential for your clinical management, then it will mean that you will have to be excluded from the study.

SARS-CoV2 mitigation risk: In compliance to the current guidelines, a risk mitigation plan is in place in all research sites. For as long as current government regulations are in place, we will use at least 2 metres distancing for all study procedures that do not require contact (e.g. consent, administration of clinical scales), and use of safety measures (including, but not limited to gloves, aprons, ffp2 and ffp3 masks, and eye protection) as per Research Sites'

Standard Operating Procedures. Before each study visit, we will ask you to undergo a swab for Lateral Flow Device (LFD) testing. LFD testing is a fast and simple way to test people who do not have symptoms of COVID-19, but who may still be spreading the virus, and provides reliable results in 30 minutes.

What are the possible risks of taking part?

Cannulation

Insertion of a cannula (tiny tube) into a vein or artery may cause brief discomfort as the cannula penetrates the skin, which is similar to the discomfort you may feel 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 can be found in the leaflet (Arterial Line insertion and care information sheet version 1 dated 03 January 2020) provided to you with this information sheet. 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, though even when this happens, the scar left over the long term is usually 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 (20%)
- Bruising (14%)

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 problems. 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.

If any of the following occur within 72 hours after the cannula was removed, you MUST consult the Study Doctor immediately. If you are unable to contact the Study Doctor, or if you cannot reach the study Doctor, you must attend the Accident & Emergency for advice/ treatment.

- 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.

Lumbar puncture / CSF collection

The most common risks of lumbar puncture are local pain at the site and a temporary headache. A local anaesthetic is injected to make the area go numb during the procedure. This stings for a couple of minutes, and then the skin goes numb. After the procedure, you will need to lie down for an hour. About 10% of people get a headache after a lumbar puncture. Usually this gets better with water and mild painkillers, but occasionally it is severe. Rarely, a second procedure similar to a lumbar puncture is needed to treat the headache. There is a slight risk of infection because the needle breaks the skin's surface, providing a possible entry point for bacteria. To reduce the risk of infection all lumbar punctures will be performed by qualified clinician in a sterile environment, as per common practise. There is a small risk of bleeding in the spinal canal, though to avoid this risk, prior to the procedure, a blood test will be conducted to screen for blood clotting disorders. During the procedure, there is a small risk of pain or tenderness in your lower back and that this pain might radiate down the back of your legs. This pain could arise when the nerves, which float in the spinal fluid, touch the sides of the needle causing them to become stimulated. If this happens it gives a feeling of tingling down the leg which might last for a few seconds.

Persistent nerve damage after a lumbar puncture is extremely rare (approximately 1 in 1000).

We will use a needle, called an atraumatic needle, that is thinner than usual to further minimize any of these side effects. The spinal cord ends about four inches above the spot where the lumbar puncture needle is inserted. Because the needle is inserted well below where the spinal cord ends, the risk of nerve damage or paralysis is extremely low.

Imaging procedures

If you take part in this study you will have up to 6 PET scans. These will be extra to those that you would have if you did not take part in the trial.

These procedures use ionising radiation to form images of your body. Ionising radiation may cause cancer many years or decades after the exposure. We are all at risk of developing cancer during our lifetime. 50% of the population is likely to develop one of the many forms of cancer at some stage during our lifetime. Taking part in this study will increase the chances of this happening by an additional 0.02%, if you will perform the [^{18}F]FDG and [^{11}C]UCB-J PET scans. If you will be in the arm of 10 MSA patients who will perform the [^{18}F]APN-1607 PET scan, this the chances of this happening will increase by an additional 0.04%.

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 willing to be on a highly effective form of contraception, and even if this is the case a urine pregnancy test prior to the PET scan will need to be performed to be sure that you can proceed to take part.

Highly effective measures of contraception are (if you are a woman of childbearing age):

- Combined (estrogen and progesterone containing) hormonal contraception associated with initiation of ovulation (oral, intravaginal, or transdermal);

- Progesterone-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable);
- Intrauterine device; Intrauterine hormone releasing system;
- Bilateral tubal occlusion;
- Vasectomized partner;
- Sexual abstinence.

If you are a male participant with female partner of child-bearing potential, you must use one of the following contraceptive methods for 90 days after each dose of radiotracer:

- Condom plus partner use of a highly effective contraceptive (see point above);
- Sexual abstinence.

The MRI scan does not expose you to ionizing radiation, but it can be noisy (we will 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), or any other implants (pacemakers, orthopaedic implants etc) you must let us know, so we can assess if the procedure will pose any risk to you. Some of the MRI sequences, called diffusion imaging, functional imaging (fMRI) and arterial spin labelling (ASL), are non-vendor 3rd party sequences. This could mean we will be using the MRI scanner off-label for these particular non-vendor sequences. These MRI sequences are provided by a third party in a 3-way agreement between the provider, the user and the Vendor. 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 artefacts, and producing better-quality data. 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. You will also have a call bell and will be able to contact the MR operator during the scan.

What are the possible benefits of taking part?

PET is not a form of treatment and does not provide any direct benefits to participants. However, the knowledge acquired from this study will improve our understanding of Multiple System Atrophy (MSA) and may help us to provide the means for the development of better drugs for this disease. As there are no alternative methods to study in vivo the brain we believe that the added risk in this study due to the additional radiation exposure is acceptable.

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, Senior Research Governance Officer (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.

In the unlikely event that you will lose your capacity during the course of the study, you would be withdrawn from the study. All identifiable data or tissue already collected with consent would be retained and used in the study. No further data or tissue would be collected or any other research procedures carried out on or in relation to you.

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 this study we will need to register you at Imperial College Healthcare NHS Trust and record minimal information about you in the Trust's medical records system.

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.

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 _____ Tel: _____ Email: _____

Study Coordinator:

Name:_____ Tel: _____ Email: _____

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 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 in Consent Form of this study. 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 London (Imanova). The funders have no commercial interest on this study. The University of Exeter is the Sponsor of the study, contact details of the Sponsor Representative are below.

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 - Westminster Research Ethics Committee. It has also been reviewed by the Health Research Authority (HRA) in order to obtain HRA Approval. The study is also assessed by each NHS Trust involved with the research in order to obtain Capacity and Capability Approval at local level.

Contact details 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 _____ Tel: _____ Email: _____

Study Coordinator:

Name:_____ Tel: _____ Email: _____

Sponsor Representative:
Ms Pam Baxter
Senior Research Governance Officer
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.

Thank you for your interest in the study and for reading the Information Sheet