NRF2 Biomarkers Study

Study reference: STH19982

Chief Investigator: Professor Dame Pamela Shaw

Participant Information Sheet - Patients

Part 1: About the study

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. Talk to others about the study if you wish.

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

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.

1. What is the purpose of the study?

Research has shown that neurodegenerative diseases cause the death of nerve cells. These conditions are very distressing for sufferers and their families. Unfortunately there is a lack of treatments available to slow disease progression and clinical trials have not been very successful, partly because there is no way to demonstrate that a drug is reaching the nervous system in the right amounts to protect the nerve cells from injury.

The purpose of this study is to investigate a pathway (sometimes called the programmed cell-life pathway) controlled by a molecule named NRF2. This molecule promotes cell survival in the face of stresses such as oxidative stress, inflammation, and failure of the energy-generating and protein quality-control pathways within neurons which are known to contribute to neurodegeneration.

Our aim is to develop imaging and body fluid markers to show NRF2 pathways working in the body. It is hoped that these results will be applied later in clinical trials to test the effectiveness of NRF2 activators (experimental drugs) for patients with Motor Neurone Disease (MND) and Alzheimer's disease (AD).

2. Why have I been invited to participate?

You will have been approached to take part in this study by the neurology team caring for you. Donating biological samples and undergoing a more detailed imaging scan will help us to learn more about motor system disorders.

You may also be a patient undergoing investigations (e.g. a lumbar puncture) but without a neurodegenerative condition. In this scenario, we would like you to participate in the study and be a 'control case'.

We are also recruiting ***healthy participants***, which may include ***partners/carers*** of people with motor system disorders. To identify markers we need to compare people who have the disorder with people who do not have the disease (control cases). These 'control cases' should ideally be similar in age and circumstances to the patients.

3. Do I have to take part?

No. It is up to you to decide whether or not to take part. If you do take part, you will be given this information sheet to keep and you will be asked to sign a consent form. You are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive now or in the future.

We will ask you if you would be willing to be contacted about other studies in the future. You can decline to be contacted and this will not impact on your ability to participate in the current study or your future clinical care.

4. What will happen to me if I take part?

If you are interested in participating, a member of the study team will speak to you about what the study involves. If you would like to take part, you will be invited to attend the Royal Hallamshire Hospital (Sheffield Teaching Hospitals NHS Foundation Trust) to discuss the study in full with a member of the study team. It may be possible to arrange this alongside your routine clinic visit.

During the study you won't be asked to stop taking any current medication or herbal substances.

If you provide consent to take part we will ask you to undergo a detailed imaging scan of your brain (MRI) on two occasions (4 months apart), and donate some biological samples as described in detail below.

a) Blood sample

An experienced phlebotomist or nurse will collect a small blood sample (up to 80 ml, the equivalent of around 4-5 tablespoons), usually from a vein in your arm. We will ask you to provide a second blood sample approximately 4 months later. The samples will be used to help determine whether we can detect changes in the NRF2 pathway over time.

b) Skin sample

We will ask if you are willing to donate a small sample of skin, usually from the inner arm. A local anaesthetic injection will be used to numb the skin. A small piece of skin, approximately 3-4 mm diameter, will be taken. The biopsy does not require stitching as it is

very small and is therefore covered with a dressing which is left in place for 2-3 days. The procedure takes approximately 10 minutes. We require a skin sample on a single occasion.

Before deciding whether to donate a skin sample, it is important that you tell the researcher about any medication you are taking and any medical conditions you have, so that they can make sure it is safe for you to take part in this part of the study.

The skin cells will be grown and may be differentiated into motor neurones or supporting cells known as glia, allowing us to carry out investigations looking at abnormal cellular functions. The skin cells we grow might be taken to collaborating laboratories, which may be outside the UK. This is to allow us to access the highly specialised skills available in the other laboratories to turn the skin cells into neuronal cells. Collaborators would only receive anonymised samples; this means that they would not have any information that would be able to identify you personally.

c) Cerebrospinal fluid (CSF)

You may be approached to take part in the study if the consultant neurologist caring for you considers that you need a test called a lumbar puncture (LP) to help in the diagnosis of your condition or as a treatment measure, or we may ask if you are willing to undergo the procedure for research purposes. This is a very routine procedure in our hospital and is only ever done by highly trained staff who have done many such procedures.

A lumbar puncture involves taking a small sample of the fluid from around the lower part of the spine with a fine needle (up to 20 ml, which is around 10-16% of the total amount, and is replaced by the body within a few hours). This procedure is done under a local anaesthetic to minimise discomfort. This is done whilst you are sitting (or lying) comfortably on a hospital bed. We suggest that you rest lying flat for 30 minutes after the procedure. You may drive afterwards. The CSF sample is then sent to various different laboratories in the hospital for analysis. If you are undergoing a lumbar puncture as part of your clinical care, we will ask your permission to take a small extra sample for research purposes.

We will ask you to provide a second CSF sample approximately 4 months later.

Your sample will be used to measure several CSF components that may be altered in patients who have a disorder of the motor system and which may affect the function of nerve cells. The effects of the CSF on nerve cells grown in the laboratory will also be measured. We need to compare any changes in the CSF composition and nerve cell growth with patients who are neurologically normal and with patients who have other neurological disorders. Therefore we are asking patients with a variety of neurological symptoms to participate in this study.

d) Magnetic resonance spectroscopy (MRS) brain scan

Magnetic resonance spectroscopy (MRS) is a detailed type of scan. The scan is based on magnetism and does not involve ionising radiation (which makes it different from an X-ray), so there is no radiation risk. Anyone can have one, as long as they don't have a pacemaker, other non-MR compatible metallic device (the magnetism from the scan can upset such devices), or metallic fragments in the eye, for example, from welding (as the magnetism could make them move and cause damage). For the purposes of this study, pregnancy

would also be considered a reason not to participate; although MRS scans can be performed in pregnancy in some circumstances, the potential risks to an unborn developing baby are still uncertain. You will be asked about these things before you go in the scanner. In the scanner, it is important you lie very still. Some people can find the scanner claustrophobic, but you have a buzzer that you can press at any time to be let out and, in Sheffield, we have recently installed a new scanner that is open at both ends. The scanner is quite noisy so you will wear either earplugs or earphones. You can listen to the radio if you wish. In order to get good results, it is important that you lie very still. The scan takes about 45-60 minutes. We will ask you to have a second scan approximately 4 months later.

Below is a table to summarise what is carried out at each study visit:

Assessment	**Baseline**	**Month 4**
a) Blood sample	**X**	**X**
a) Skin sample	**X**	
b) CSF sample (lumbar puncture)	**X**	**X**
c) MR scan	**X**	**X**

We will ask your permission to periodically access relevant sections of your medical records whilst the study is on-going, to verify information about your current health.

Expenses and payments:
Reasonable travel expenses that you have incurred due to your participation will be reimbursed – please discuss with the research team for further details.

5. What are the possible benefits of taking part?
There is no intended clinical benefit to you for taking part in this study. We cannot promise the study will help you but we hope that the information we obtain will eventually help to improve the diagnosis and treatment of people with motor system disorders.

6. What are the possible disadvantages and risks of taking part?
Blood samples:
There are small risks associated with needle injections. For most people, needle injections do not cause serious problems, however some people experience a small amount of swelling, bleeding or pain at the needle site or some people may feel faint. On very rare occasions infection may occur.

Skin samples:
The biopsy itself is done following a local anaesthetic injection to numb the biopsy site. You should therefore not feel anything. Some patients however may feel some mild discomfort. There can be bruising around the biopsy site. The biopsy site may heal with a small scar.

CSF samples:
The spinal fluid removal procedure (or LP) is generally a very safe and trouble-free procedure. Although many people understandably worry beforehand that it might be very uncomfortable, this is not our usual experience, and highly-trained doctors and nurses perform this procedure routinely without any complications. LP can be briefly painful when

the local anaesthetic is applied under the skin of the lower back, and occasionally as the needle is passed into the space between the bones it can cause a momentary feeling like an electric shock in your legs. In practice, when carried out by experienced staff (as it would be), there is rarely any significant discomfort for patients.

The removal of spinal fluid can however sometimes result in a temporary headache the day after the procedure. The headache occur because of temporary low spinal fluid pressure due to leaking fluid from the needle hole, and is recognisable because it is better lying down. This complication affects 5-10% of patients to a mild extent. It is more common in those under 40 years of age. In rare cases the headache is persistent or severe enough to keep a person in bed for several days, and extremely rarely requires a second procedure to try to seal the hole preventing further fluid leak, known as a blood patch. In practice LPs are carried out on a daily basis at the Sheffield Teaching Hospitals NHS Foundation Trust without complications, and all the necessary facilities and staff are available to deal with any unexpected problems.

MRS scans:
Sometimes people can feel claustrophobic, breathless or generally unwell in the scanner, but you will have a buzzer which you can press at any time to be let out for any reason. In addition, the new scanner in Sheffield has quite a large bore.

There is a small chance that having a scan could result in us finding an unexpected abnormality which was causing no major symptoms, for example, an aneurysm or small tumour. If this were to occur, deciding what to do about the abnormality could be difficult. In these circumstances, you would be informed of the abnormality and referred on to the relevant specialist for further assessment and discussion of treatment options. You should consider carefully this potential risk before you decide whether you wish to take part in this study.

This completes Part 1 of the Information Sheet.

If the information in Part 1 has interested you and you would like to consider participating in the study, please continue to read the additional information in Part 2 before making a decision.

Part 2: Additional information

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

You can withdraw from the study at any time, without giving a reason. Your decision to withdraw will not affect your future care in any way. If you choose to withdraw from the study at any point, any data collected from you up until that time will continue to be used. Any remaining sample(s) will be destroyed if you request this, but data from any analysis that has already performed on your samples will continue to be used.

8. What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. If you have a concern about any aspect of this study, you should ask to speak with the researchers who will do their best to answer your questions. You can contact Liam Haslam on 0114 271 3339 or Lee Tuddenham on 0114 222 2263 in the first instance. If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure or by contacting the Patient Services Team, Sheffield Teaching Hospitals NHS Foundation Trust, Glossop Road, Sheffield, S10 2JF, Tel: 0114 2712400, email: PST@sth.nhs.uk.

Sheffield Teaching Hospitals NHS Foundation Trust, as Sponsor, has appropriate insurance in place in the unlikely event that you suffer any harm as a direct consequence of your participation in this trial.

9. Will my taking part in this study be kept confidential?

Yes. All the information about your participation in this study will be kept confidential.

Please note that the study team is made up of staff working for both the NHS Trust and the University of Sheffield (all of whom may have access to your data).

Sheffield Teaching Hospitals NHS FT (STH NHS FT) is the 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 controller for this study. This means that we are responsible for looking after your information and using it properly. We will keep identifiable information about you for 5 years after the study has finished.

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

You can find out more about how we use your information at https://www.sheffieldclinicalresearch.org/ or by contacting the study team.

If you wish to raise a complaint on how we have handled your personal data, you can contact our Data Protection Officer who will investigate the matter. If you are not satisfied with our response or believe we are processing your personal data in a way that is not

lawful you can complain to the Information Commissioner's Office (ICO). Our Data Protection Officer is Peter Wilson and you can contact them by phone (0114 2265153) or email *(Peter.Wilson@sth.nhs.uk).*

STH NHS FT / University of Sheffield will use your name, NHS Number 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.

If you join the study, individuals from STH NHS FT / University of Sheffield and regulatory organisations may look at your medical and research records to check the accuracy of the research study. The only people in STH NHS FT / University of Sheffield who will have access to information that identifies you will be people who need to contact you about the research study or audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number or contact details.

All study personnel will have a duty of confidentiality to you as a research participant and nothing that could reveal your identity will be disclosed outside the research site. We will ask you to consent to allow these people access to the information collected about you in the course of the study. All people looking at your records, and the procedures for handling, processing, storage and destruction of your data are compliant with Data Protection Regulations.

You will only be identified on your donated samples and study documentation using a unique study code that will be assigned to you. It will not be possible for anyone to be able to identify you from the samples or study database as all the data will be coded. Only the study team will be able to link you to the data in the study database. Any information that could identify you personally will be stored in locked offices at the study site.

Anonymised data collected during the course of the study may be passed on to other organisations, which may include commercial organisations.

10. Will my General Practitioner (GP) / family doctor be involved?

We will not routinely inform your GP about your participation in the study, but will ask your permission to contact your doctor if we find any clinically relevant results, or if you experienced a complication of one of the procedures, for example, a headache after the lumbar puncture. You will be asked to consent to allow us to do this and also for your GP to verify any information that you tell us about your medical history if required.

11. What will happen to any samples I give?

The sample(s) that you give will be for research purposes (which will include DNA analysis) and will be considered as a gift. Samples will be labelled with the study code, date and volunteer identifier only and it will not be possible to identify who you are from your samples alone.

Any sample remaining after the study has ended may be stored indefinitely in a licensed tissue bank. You will be asked to consent for us to be able to use your stored samples in the future for health research. Occasionally, the study team may send some of your sample for

analysis to other laboratories, possibly outside the United Kingdom. All samples will be anonymised, which means that the person analysing your sample will not be able to identify you.

12. What will happen to the results of the research study?

The results of this research may be presented at scientific meetings in the UK and overseas. It will not be possible to identify you from any of the data that will be presented. The data from the study may also be published in a medical journal. You will not be identified in any report or publication. The results of this study may lead to the development of patents and/or to commercial benefits for sponsors and researchers. A patent is a right to the exclusive use of an invention, such as a new test or new drug, for a fixed period of time. You would not be entitled to receive any financial benefit.

13. Who is organising the research?

This research study is a collaboration between researchers at the University of Sheffield and Sheffield Teaching Hospitals NHS Foundation Trust.

14. Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by the Yorkshire and Humber Sheffield Ethics Committee.

15. Contact Details:

Further information about this study can be obtained from Liam Haslam on 0114 271 3339 or email Liam.Haslam@sth.nhs.uk; or Lee Tuddenham on 0114 222 2263 or email L.tuddenham@sheffield.ac.uk.

If you would like to talk to somebody who is independent from this study, to discuss volunteering in research, please contact the NHS Patient Services Team (PST) on [0114 2712400] or by emailing (PST@sth.nhs.uk).

Thank you for reading this information sheet and considering taking part in this study.
If you decide to take part you will be given a copy of this information sheet and the signed consent form to take home with you and keep.